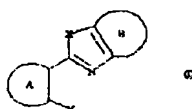


**(54) Title of invention**

Heterocyclic derivatives

**(57) Abstract (Amended).****Method of Solution**

Heterocyclic derivatives represented by the general formula (I) or the pharmaceutically acceptable salt thereof



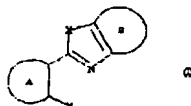
[wherein, ring A and ring B respectively denote aromatic rings, and -X- denotes -NR<sup>O</sup>-, -S- or -O- and R<sup>O</sup> denotes hydrogen atom or lower alkyl group, and -Y is (1) -NR<sub>1</sub>R<sub>2</sub> (wherein, R<sub>1</sub> denotes a lower alkyl group, lower alkenyl group or lower alkynyl group, and R<sub>2</sub> denotes organic group other than lower alkyl group. Or R<sub>1</sub> and R<sub>2</sub>, together with nitrogen atom, may form a saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group), (2) -C(=O)-NR, (3) -C(OH)R or (4) a saturated or unsaturated 5-7 membered heterocyclic group which may be substituted].

**Effect**

The compound of general formula (I) has osteoclast differentiation induction inhibition and is useful as anti-inflammatory drug, antirheumatic and therapeutic drug of disease accompanied by bone regeneration insufficiency.

**Patent Claims****Claim 1**

A heterocyclic derivative represented by formula (I) or the pharmaceutically acceptable salt thereof



[wherein, ring A and ring B each independently denote a substituted or unsubstituted aromatic ring, and -X- denotes -NR<sup>O</sup>-, -S- or -O- and R<sup>O</sup> denotes hydrogen atom or lower alkyl group, and -Y is

(1) -NR<sub>1</sub>R<sub>2</sub>

(wherein, R<sub>1</sub> denotes an optionally substituted lower alkyl group, an optionally substituted lower

alkenyl group or optionally substituted lower alkynyl group, and R2 denotes organic group except lower alkyl group. Or R1 and R2, together with nitrogen atom, may form a saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group),

(2)  $-C(=O)-NR^1R^2$

(wherein, R1' and R2' each independently denote an optionally substituted lower alkyl group. Or R1' and R2' may form saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group together with nitrogen atom), (3)  $-C(OH)R^1R^2$

(wherein, R1" and R2" each independently denote an optionally substituted lower alkyl group) or

(4) a saturated or unsaturated 5-7 membered heterocyclic group which may be substituted.

#### Claim 2

A heterocyclic derivative in accordance with Claim 1 or pharmaceutically acceptable salts thereof wherein in formula (I), -R2 is represented by following formulae (a)-(g)

(a) -R3

(b) -D-R3

(c)  $-(D)_n-E-F-R3$

(d)  $-C(=O)-CR^6R^7-NR^8-D-R3$

(e)  $-C(=O)-CR^6R^7-NR^8-C(=O)-CR^6R^7-NR^8-D-R3$

(f)  $-C(=O)-CR^6R^7-NR^8-R9$

(g)  $-C(=O)-CR^6R^7-NR^8-C(=O)-CR^6R^7-NR^8-R9$

(in the formula, -D- denotes  $-C(=O)-$ ,  $-C(=O)-O-$ ,  $-C(=O)-NR^4-$  or  $-S(=O)_2-$ . -E- denotes an alkylene, alkenylene or alkynylene. -F- is  $-O-$ ,  $-O-C(=O)-$ ,  $-C(=O)-O-$ ,  $-NR^5-$ ,  $-NR^5-C(=O)-$ ,  $-C(=O)-NR^5-$ ,  $-NR^5-C(=O)-O-$ ,  $-S(=O)_2-NR^5-$  or  $-NR^5-S(=O)_2-$ , and R4, R5, R8 and R8' may be the same or different and denote hydrogen atom, an optionally substituted lower alkyl group, lower alkenyl group or lower alkynyl group. n is 0 or 1. R3 in (a) means an optionally substituted lower cycloalkyl group, an optionally substituted aryl group, formyl group or cyano group, R3 in (b) to (e) denotes an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, an optionally substituted lower cycloalkyl group, an optionally substituted aryl group or a saturated or unsaturated heterocyclic group,

R6, R6' and R9 denote a hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, an optionally substituted lower cycloalkyl group, an optionally substituted aryl group or a saturated or unsaturated heterocyclic group.

R7 and R7' are hydrogen atom or the lower alkyl group which may be substituted. Moreover, R6 and R7, R6' and R7' may be linked to form an optionally substituted, an optionally substituted  
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cycloalkene or a saturated or unsaturated heterocycle which may be substituted. Moreover, R6 and R8, R6' and R8', R8 and R9, R8' and R9' may be linked to form a saturated or unsaturated heterocycle which may be substituted), or R2, together with R1, may form a saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group.

**Claim 3**

A heterocyclic derivative in accordance with Claim 2 or pharmaceutically acceptable salts thereof wherein in (formula 1), ring A and ring B are each independently substituted or unsubstituted 6 membered aromatic ring including 0-2 nitrogen atom, and -X- is -NH-, R1 is lower alkyl group, -R2 is represented by following formulae (a)-(e)

(a) -R3

(b) -D-R3

(c) -(D)n-E-F-R3

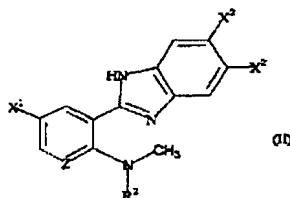
(d) -C(=O)-CR6R7-NR8-D-R3

(e) -C(=O)-CR6R7-NR8-R9

(wherein, D is -C(=O)- or -C(=O)-O-, and n is 0 or 1. E, F, R3, R6, R7, R8 and R9 have the same aforesaid meanings), or R2, together with R1, may form a saturated or unsaturated 5-6 membered heterocycle which may be substituted by oxo group.

**Claim 4**

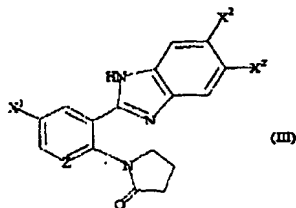
A heterocyclic derivative in accordance with Claims 1-3 represented by formula (II) or pharmaceutically acceptable salts thereof



(wherein, X1 denotes a hydrogen atom, halogen atom, cyano group or lower alkyl group. X2, X2' each independently denote a hydrogen atom, a halogen atom or a lower alkyl group. Z denotes -CH= or nitrogen atom. R2 has the same aforesaid meaning).

**Claim 5**

A heterocyclic derivative in accordance with Claims 1-3 represented by formula (III) or pharmaceutically acceptable salts thereof



(wherein, X1, X2, X2' and Z have the same aforesaid meanings).

**Claim 6**

A drug containing as effective ingredient heterocyclic derivative in accordance with any of Claims 1-5 or pharmaceutically acceptable salts thereof.

**Claim 7**

An osteoclast differentiation induction inhibitor and/or bone destruction inhibitor containing as effective ingredient a heterocyclic derivative in accordance with any of Claims 1-5 or a pharmaceutically acceptable salt thereof.

**Claim 8**

An anti-inflammatory drug, an antirheumatic and/or a therapeutic drug of diseases accompanied by bone regeneration insufficiency containing as effective ingredient a heterocyclic derivative in accordance with any of Claims 1-5 or a pharmaceutically acceptable salt thereof.

**Detailed Description of the Invention**

**(0001)**

Technical Sphere of the Invention

This invention relates to the following, namely, novel heterocyclic derivatives. More particularly, this invention relates to a heterocyclic derivative which can be used as a therapeutic drug of inflammatory diseases such as rheumatism or the like and to a drug containing as effective ingredient the aforesaid compound.

**(0002)**

Technology of the Prior Art

In the prior art, many non-steroidal anti-inflammatory drugs are used as anti-inflammatory agents and antirheumatics. These drugs are said to be effective because they hinder cyclooxygenase and prevent biosynthesis of prostaglandin (Allergy Clin. Immunol., Vol. 58, p. 691 (1976)). Moreover in many novel non-steroidal anti-inflammatory drugs, the agents which hinder cyclooxygenase have been explored. However, although non-steroidal anti-inflammatory

drugs of the prior art have the action to reduce the swelling and pain of inflammation, they cannot prevent the progress of osseous tissue destruction in arthritis. In addition, side effects such as gastrointestinal tract disorder or the like often become problems in particular in the case of long-term administration. A novel drug having essential inflammation therapeutic effect having osseous tissue destruction inhibitory action, and without any side effect, has not been known. Moreover, as a drug having benzimidazole skeleton, benzthiazole skeleton or benzoxazole skeleton, N-[2-(1H-benzimidazol-2-yl) phenyl] methoxy acetamide, N-phenyl amide compound or the like having antispasmodic action are described in Kokai 8-73438, US5,496,826 (Watson, et al., March 5, 1996). Moreover, in Kokai 2000-281577, 2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) anilino]-N,N'-dimethylacetamide having proteoglycan formation promotion action is disclosed, a phenyl benzimidazole compound substituted by alkyl amide group useful as antitumor drug and antibacterial drug is disclosed in Kokai 8-231514, a benzimidazole compound substituted by methoxyphenyl group or methylphenyl having tachykinin antagonism is disclosed in Kohyo 2000-506529. However, the compound of this invention having osseous tissue destruction inhibitory action is not disclosed in the said literature. Moreover, a process for the production of N-[2-(1H-benzimidazol-2-yl) phenyl]-N,N'-dimethylamine is disclosed in J, Lumin. 249 (1999), and it is disclosed in J, Med, Chem. 697 (1970) that the said compound has antiviral action, however, the osteoclast differentiation induction inhibitory action is not described at all.

(0003)

Problems to be Overcome by Invention

The object of this invention is a creation of novel drug having osteoclast differentiation induction inhibitory action.

(0004)

Means to Overcome these Problems

Differentiation induction of osteoclast is found in rheumatic arthritis site, and it is reported that bone destruction is proceeding by osteoclast. These inventors searched for a compound having osteoclast differentiation induction inhibition using osteoclast differentiation induction system reported in Japan bone metabolism official journal of scientific society (Japan bone metabolism official journal of scientific society, Vol. 12, p. 188 (1994)) and as a result, discovered that a group of heterocyclic derivatives having benzimidazole and the like had a potent action. This invention was completed based on this discovery.

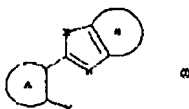
(0005)

In other words, this invention relates to a heterocyclic derivative having following general formula (I) or pharmaceutically acceptable salts thereof, and moreover, a drug containing this as effective ingredient.

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[1] A heterocyclic derivative represented by formula (I) or the pharmaceutically acceptable salt thereof



[wherein, ring A and ring B each independently denote a substituted or unsubstituted aromatic ring, and -X- denotes -NR<sup>O</sup>-, -S- or -O- and R<sup>O</sup> denotes hydrogen atom or lower alkyl group, and -Y is

(1) -NR<sup>1</sup>R<sup>2</sup>

(wherein, R<sup>1</sup> denotes an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group or optionally substituted lower alkynyl group, and R<sup>2</sup> denotes organic group except lower alkyl group. Or R<sup>1</sup> and R<sup>2</sup>, together with nitrogen atom, may form saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group),

(2) -C(=O)-NR<sup>1</sup>'R<sup>2</sup>'

(wherein, R<sup>1</sup>' and R<sup>2</sup>' each independently denote an optionally substituted lower alkyl group. Or R<sup>1</sup>' and R<sup>2</sup>' may form saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group together with nitrogen atom), (3) -C(OH)R<sup>1</sup>"R<sup>2</sup>"

(wherein, R<sup>1</sup>" and R<sup>2</sup>" each independently denote an optionally substituted lower alkyl group) or

(4) a saturated or unsaturated 5-7 membered heterocyclic group which may be substituted.

[2] A heterocyclic derivative in accordance with [1] or pharmaceutically acceptable salts thereof wherein in formula (I), -R<sup>2</sup> is represented by following formulae (a)-(g)

(a) -R<sup>3</sup>

(b) -D-R<sup>3</sup>

(c) -(D)<sub>n</sub>-E-F-R<sup>3</sup>

(d) -C(=O)-CR<sup>6</sup>R<sup>7</sup>-NR<sup>8</sup>-D-R<sup>3</sup>

(e) -C(=O)-CR<sup>6</sup>R<sup>7</sup>-NR<sup>8</sup>-C(=O)-CR<sup>6</sup>'R<sup>7</sup>'-NR<sup>8</sup>'-D-R<sup>3</sup>

(f) -C(=O)-CR<sup>6</sup>R<sup>7</sup>-NR<sup>8</sup>-R<sup>9</sup>

(g) -C(=O)-CR<sup>6</sup>R<sup>7</sup>-NR<sup>8</sup>-C(=O)-CR<sup>6</sup>'R<sup>7</sup>'-NR<sup>8</sup>'-R<sup>9</sup>

(in the formula, -D- denotes -C(=O)-, -C(=O)-O-, -C(=O)-NR<sup>4</sup>- or -S(=O)<sub>2</sub>-. -E- denotes an alkylene, alkenylene or alkynylene. -F- is -O-, -O-C(=O)-, -C(=O)-O-, -NR<sup>5</sup>-, -NR<sup>5</sup>-C(=O)-, -C(=O)-NR<sup>5</sup>-, -NR<sup>5</sup>-C(=O)-O-, -S(=O)<sub>2</sub>-NR<sup>5</sup>- or -NR<sup>5</sup>-S(=O)<sub>2</sub>-, and R<sup>4</sup>, R<sup>5</sup>, R<sup>8</sup> and R<sup>8</sup>' may be the same or different and denote hydrogen atom, an optionally substituted lower alkyl group, lower alkenyl group or lower alkynyl group. n is 0 or 1. R<sup>3</sup> in (a) means an optionally substituted

lower cycloalkyl group, an optionally substituted aryl group, formyl group or cyano group,

R3 in (b) to (e) denote an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, an optionally substituted lower cycloalkyl group, an optionally substituted aryl group or a saturated or unsaturated heterocyclic group,

R6, R6' and R9 denote a hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted lower alkenyl group, an optionally substituted lower alkynyl group, an optionally substituted lower cycloalkyl group, an optionally substituted aryl group or a saturated or unsaturated heterocyclic group.

R7 and R7' are each hydrogen atom or a lower alkyl group which may be substituted. Moreover, R6 and R7, R6' and R7' may be linked to form an optionally substituted cycloalkane, an optionally substituted cycloalkene or a saturated or unsaturated heterocycle which may be substituted. Moreover, R6 and R8, R6' and R8', R8 and R9, R8' and R9' may be linked to form a saturated or unsaturated heterocycle which may be substituted, or R2 may form a saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group together with R1.

[3] A heterocyclic derivative in accordance with [2] or pharmaceutically acceptable salts thereof wherein in (formula 1), ring A and ring B are each independently substituted or unsubstituted 6 membered aromatic ring including 0-2 nitrogen atom, and -X- is -NH-, R1 is lower alkyl group, - R2 is represented by following formulae (a)-(e)

(a) -R3

(b) -D-R3

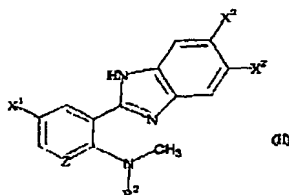
(c) -(D)n-E-F-R3

(d) -C(=O)-CR6R7-NR8-D-R3

(e) -C(=O)-CR6R7-NR8-R9

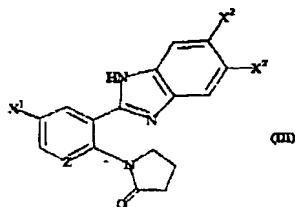
(wherein, D is -C(=O)- or -C(=O)-O-, and n is 0 or 1. E, F, R3, R6, R7, R8 and R9 have the same aforesaid meaning), or R2 may form saturated or unsaturated 5-6 membered heterocycle which may be substituted by oxo group together with R1.

[4] A heterocyclic derivative in accordance with [1]-[3] represented by formula (II) or pharmaceutically acceptable salts thereof



(wherein, X1 denotes a hydrogen atom, halogen atom, cyano group or lower alkyl group. X2, X2' each independently denote a hydrogen atom, halogen atom or lower alkyl group. Z denotes -CH= or nitrogen atom. R2 has the same aforesaid meaning).

[5] A heterocyclic derivative in accordance with [1]-[3] represented by formula (III) or pharmaceutically acceptable salts thereof



(wherein, X1, X2, X2' and Z have the same aforesaid meanings).

[6] A drug containing as effective ingredient heterocyclic derivative in accordance with any of [1]-[5] or a pharmaceutically acceptable salt thereof.

[7] An osteoclast differentiation induction inhibitor and/or bone destruction inhibitor containing as effective ingredient heterocyclic derivative in accordance with any of [1]-[5] or a pharmaceutically acceptable salt thereof.

[8] An anti-inflammatory drug, antirheumatic and/or therapeutic drug of disease accompanied by bone regeneration insufficiency containing as effective ingredient heterocyclic derivative in accordance with any of [1]-[5] or a pharmaceutically acceptable salt thereof.

(0006)

#### The definition of substituents

In this specification, "halogen atom" means fluorine, chlorine, bromine or iodine. Lower alkyl in "lower alkyl group", "lower alkoxy group", "lower alkyl thio group", "lower alkoxy carbonyl group", "lower alkyl carbonyl group", "lower alkyl carbonyl oxy group", "lower alkyl sulphenyl group" or "lower alkyl sulphonyl group" means a straight or branched chain alkyl of 1-6C. In other words, as "lower alkyl group", methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, t-butyl group, pentyl group, iso pentyl group, 2-methylbutyl group, neopentyl group, 1-ethyl propyl group, hexyl group, 4-methyl pentyl group, 3-methyl pentyl group, 2-methyl pentyl group, 1-methyl pentyl group, 3,3-dimethylbutyl group, 2,2-dimethylbutyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group are exemplified. As "lower alkoxy group", methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy



group, iso butoxy group, sec-butoxy group, t-butoxy group, pentyloxy group, iso pentyloxy group, 2-methyl butoxy group, neopentyl oxy group, 1-ethyl propoxy group, hexyloxy group, 4-methyl pentyloxy group, 3-methyl pentyloxy group, 2-methyl pentyloxy group, 1-methyl pentyloxy group, 3,3-dimethyl butoxy group, 2,2-dimethyl butoxy group, 1,1-dimethyl butoxy group or the like are exemplified. As "lower alkyl thio group", methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutyl thio group or the like are exemplified. As "lower alkoxy carbonyl group", methoxycarbonyl group, ethoxycarbonyl group, propoxy carbonyl group, isopropoxy carbonyl group, t-butoxycarbonyl group, n-butoxycarbonyl group or the like are exemplified. As "lower alkyl carbonyl group", acetyl group, propionyl group, butanoyl group, isobutanoyl group, pentanoyl group, hexanoyl group or pivaloyl group or the like are exemplified. As "lower alkyl carbonyl oxy group", acetoxy group, propionyloxy group, pentanoyloxy group or the like are exemplified. As "lower alkyl sulphonyl group", methanesulphonyl group, ethane sulphonyl group, propane sulphonyl group, isobutane sulphonyl group or the like are exemplified. As "lower alkyl sulphenyl group", methane sulphenyl group, ethane sulphenyl group, propane sulphenyl group, isobutane sulphenyl group or the like are exemplified. "Lower alkenyl group" means straight or branched chain alkenyl group of 2-6C, and vinyl group, aryl group, butenyl group or the like can be exemplified. "Lower alkynyl group" means straight or branched chain alkynyl group of 2-6C, and propargyl group, ethynyl group or the like can be exemplified.

(0007)

As "substituted or unsubstituted aromatic ring", for example aromatic ring of ring component atoms 5-14 is nominated, and in an embodiment, benzene ring, naphthalene ring, pyridine ring, pyrazine ring, pyrimidine ring, pyridazine ring, quinoline ring, isoquinoline ring, quinazoline ring, quinoxaline ring, thiophene ring, pyrrole ring, furan ring, benzo thiophene ring, benzofuran ring, indole ring, imidazole ring, pyrazole ring, isoxazole ring, iso thiazole ring, thiazole ring, oxazole ring, benzimidazole ring, benz thiazole ring or benzoxazole ring or the like is nominated. "Aryl group" is a monovalent group wherein nitrogen atom or carbon atom on the aforesaid "substituted or unsubstituted aromatic ring" comprise bond position. As "saturated or unsaturated heterocycle", for example saturated or unsaturated 1-3 ring 5-7 membered heterocyclic group containing the sulphur atom which may be oxidised with 1-6 nitrogen atom, oxygen atom and/or 1 or 2 oxygen atom is nominated, and in an embodiment, furan, tetrahydrofuran, pyran, tetrahydropyran, thiophene, thiophene 1,1-dioxide, pyrrole, thiazole, pyrazole, oxazole, imidazole, tetrazole, isoxazole, iso thiazole, triazole, indole, benzo thiophene, benzofuran, pyridine, pyrrolidine, pyrazine, pyrimidine, pyridazine, triazine, quinoline, isoquinoline, morpholine, thiomorpholine, thiomorpholine 4-oxide, piperazine, piperidine, or the like. "Saturated or unsaturated heterocyclic group" is a monovalent group wherein nitrogen atom or carbon atom on the aforesaid "substituted or unsubstituted heterocycle" comprise bond position.

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"Cycloalkane" means cyclo C3-7 alkyl, namely cyclopropane, cyclobutane, cyclopentane, cyclohexane or the like. "Lower cycloalkyl group" is a monovalent group of the aforesaid "cycloalkane". "Lower cycloalkyl oxy group", "lower cycloalkyl carbonyl group", "lower cycloalkyl carbonyl oxy group", "lower cycloalkyl oxycarbonyl group" respectively denote oxy group in which lower cycloalkyl group is bonded, carbonyl group, carbonyl oxy group, oxycarbonyl group. "Cycloalkene" means cyclo C5-7 alkene, in other words, cyclohexene, cyclopentene or the like. As "lower cycloalkenyl group", it is a monovalent group of the aforesaid "cycloalkene". As "lower cycloalkenyl oxy group", "lower cycloalkenyl carbonyl group", "lower cycloalkenyl carbonyl oxy group", "lower cycloalkenyl oxycarbonyl group", respectively denote oxy group in which lower cycloalkyl group is bonded, carbonyl group, carbonyl oxy group, and oxycarbonyl group.

## (0008)

"Alkylene" means a straight chain or branched saturated divalent group of carbon number 1-6, for example, methylene, 1,2-ethylene, 1,1-ethylene, trimethylene, 2-methyl trimethylene, tetramethylene, pentamethylene, hexamethylene and the like are nominated. "Alkenylene" means a straight or branched chain divalent group with carbon number 2-6 having 1-2 double bond, and for example cis or trans vinylene, vinylidene, cis or trans-1-propenylene, cis or trans-2-butyne, cis or trans-3-butyne, cis or trans-1-pentenylene, cis or trans-2-pentenylene, cis or trans-3-pentenylene, cis or trans-4-pentenylene and the like are nominated. "Alkynylene" means straight or branched chain divalent group of carbon number 2-6 having 1-2 triple bond, and for example, ethynylene, propynylene, 2-butyne, 3-pentyne, 4-methyl-3-pentyne and the like are nominated.

## (0009)

"Lower haloalkyl group" is a lower alkyl group substituted by 1-5 halogen atoms which may be the same or different, and trifluoromethyl, 2-trifluoroethoxy, chloromethyl, 2-chloroethyl or the like are nominated. "Lower haloalkoxy group" is lower alkoxy group substituted by 1-5 halogen atoms which may be the same or different, and trifluoromethoxy, 2-chloroethoxy, 2-trifluoroethoxy or the like are nominated.

## (0010)

Explanation of formula (I)

In ring A of general formula (I), the ideal species for "substituted or unsubstituted aromatic ring" is 5 or 6 membered ring aromatic ring including nitrogen atom 0-2, and preferably benzene ring, pyridine ring, pyrimidine ring, thiazole ring or imidazole ring or the like is nominated, and in particular pyridine ring or benzene ring are ideal. In ring B, the ideal species for "substituted or unsubstituted aromatic ring" is 6 membered ring aromatic ring including 0-2 nitrogen atoms, and  
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preferably benzene ring or pyridine ring or the like are nominated, and benzene ring is in particular ideal. As suitable substituents of aromatic ring when the ring A / ring B is substituted, arbitrary group included in each of the following group a) or b) are nominated, and one or plurality of these may be arbitrarily substituted.

- a) Halogen atom, nitro group, cyano group, carboxyl group, sulphamoyl group, hydroxy group, carbamoyl group
- b) Lower alkyl group, lower alkoxy group, lower alkyl thio group, lower alkyl carbonyl group, lower alkoxy carbonyl group, carbamoyl group, lower alkyl sulphonyl group (each group of this group may be substituted by 1 or plurality of group arbitrarily selected from group such as halogen atom, cyano group, hydroxy group or carboxyl and the like).

In particular ideal substituent is halogen atom, cyano group, hydroxy group, carboxyl group, lower alkoxy carbonyl group, lower alkyl sulphonyl group, lower alkyl group, lower haloalkyl group, lower alkoxy group, lower haloalkoxy group, lower alkyl thio group. Even more preferable substituent as substituent of ring A is halogen atom, cyano group, carboxyl group, lower alkyl sulphonyl group, lower alkyl group, lower alkoxy group, lower alkyl thio group, and preferably these are one or two substituted. In an embodiment, fluorine atom, chlorine atom, bromine atom, methyl group, ethyl group, methoxy group, methylthio group, cyano group. Even more preferable substituent as substituent of ring B is halogen atom, lower alkyl group, lower haloalkyl group, and preferably these are one or two substituted. In an embodiment, fluorine atom, chlorine atom, bromine atom, methyl group, ethyl group, trifluoromethyl group, and chlorine atom is in particular ideal.

(0011)

In formula (I), X is preferably -NR<sup>O</sup>- and preferred R<sup>O</sup> is hydrogen atom, methyl group, and ethyl group. In particular ideal R<sup>O</sup> is hydrogen atom.

(0012)

When Y is an "optionally substituted saturated or unsaturated 5-7 membered heterocyclic group", preferably Y is 2-imidazolyl group, 5-tetrazolyl group, 2-pyridyl group, 3-pyridyl group, or 4-pyridyl group. In Y, as substituent of lower alkyl group in R1, R1', R2', R1'', R2'', R4, R5, R7, R7', R8 or R8', arbitrary group including in each group of the following a) or b) are nominated and these may be arbitrarily substituted by 1 or in plurality.

- a) Halogen atom, cyano group, hydroxy group, carboxyl group, carbamoyl group
- b) Lower alkyl group, lower alkoxy group, lower alkyl carbonyl group, lower alkyl carbonyl oxy group, lower alkoxy carbonyl group, lower alkyl thio group (each group of this group may be
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substituted by 1 or plurality of group arbitrarily selected from for example halogen atom, cyano group, group, hydroxy group, carboxyl group and the like).

(0013)

As substituent of lower alkenyl group or lower alkynyl group in R1, R4, R5, R8 or R8', the same substituents as the said lower alkyl group are nominated. As "saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group" which is formed by R1 and R2 or R1' and R2' with nitrogen atom, a pyrrole, pyrrolidine, imidazole, pyrazole, triazole, piperidine, piperazine, pyrazolidine, pyrazoline, pyrroline, piperazino or the like are ideal. Furthermore preferred substituent is hydroxy group or oxo group. As "saturated or unsaturated 5-7 membered heterocycle which may be substituted by halogen atom, hydroxy group or oxo group" which is formed by R1 and R2 with nitrogen atom, more preferably pyrrolidine and pyrroline which may be respectively unsubstituted or substituted by oxo group, hydroxy group are nominated. Among these, 2-oxopyrrolidin, 2-oxo 3-pyrroline are nominated as in particular ideal. Moreover, as ideal R1, in embodiments, methyl group, ethyl group, methoxy group, ethoxy group, 3-propenyl group are nominated. In particular ideal one is methyl group. As ideal R1', R2', R1" or R2", lower alkyl group such as methyl group, ethyl group or the like is nominated.

(0014)

As ideal example of R4 or R5, hydrogen atom, methyl group, ethyl group are nominated. As ideal example of R7, R7', R7, R7', hydrogen atom or methyl group, ethyl group are nominated. Moreover, as other ideal example, a case wherein R7, R7' respectively form "optionally substituted cycloalkane" or "saturated or unsaturated heterocycle which may be substituted" together with R6, R6'. As "preferred substituent", following a) or b) are nominated.

a) Halogen atom, cyano group, oxo group, hydroxy group or the like are nominated.

b) Lower alkyl group, lower alkoxy group

(each group of this group may be substituted by 1 or plurality of group arbitrarily selected from for example halogen atom, cyano group, group, hydroxy group, carboxyl group and the like)

As in particular desirable "cycloalkane which may be substituted", cyclobutane, cyclopentane, cyclohexane. As in particular preferred "cycloalkane which may be substituted", as "optionally substituted 5-7 membered heterocycle" pyrrolidine, piperidine, piperazine, pyrazolidine, pyrazoline, piperazino or the like are ideally exemplified.

(0015)

As ideal example of R8 or R8', methyl group, ethyl group or the like is nominated. Moreover, as "optionally substituted saturated or unsaturated 5-7 membered heterocycle" formed by R8, R8' ©Rising Sun Communications Ltd. <http://www.risingsun.co.uk>

respectively together with R6, R6', R9, pyrrolidine, piperidine, piperazine, pyrazolidine, pyrazoline, piperazino, azetidine, thiazolidine or the like are ideal. As preferred substituent, following a) or b) is nominated.

a) Halogen atom, cyano group, oxo group, hydroxy group, or the like are nominated.

b) Lower alkyl group, lower alkoxy group

(each group of this group may be substituted by 1 or plurality of group selected arbitrarily from for example halogen atom, cyano group, group, hydroxy group, carboxyl group and the like)

R6, R6' and R9, preferably may be the same or different and are hydrogen atoms or optionally substituted lower alkyl groups.

(0016)

In R3, R6, R6', R9, arbitrary group including in each group from the following a) to e) are nominated as substituent of lower alkyl group, and the lower alkyl group may be arbitrarily substituted by 1 or plurality of these.

a) Halogen atom, cyano group, mercapto group, carboxyl group, hydroxy group, sulpho group, oxo group, thioxo group, an optionally substituted amino group, an optionally substituted guanidino group, acyl group, acyl oxy group, an optionally substituted carbamoyl group, an optionally substituted sulphamoyl group, an optionally substituted ureide group

b) lower cycloalkyl group, lower cycloalkyl oxy group, lower cycloalkyl carbonyl group, lower cycloalkyl carbonyl oxy group, lower cycloalkyl oxycarbonyl group, lower cycloalkenyl group, lower cycloalkenyl oxy group, lower cycloalkenyl carbonyl group, lower cycloalkenyl carbonyl oxy group, lower cycloalkenyl oxycarbonyl group

(each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as for example halogen atom, cyano group, mercapto group, oxo group, thioxo group, lower alkyl group, lower haloalkyl group, an optionally substituted amino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, acyl group, acyl oxy group, lower alkyl thio group, carboxy-group, an optionally substituted carbamoyl group, lower alkoxycarbonyl group and the like).

(0017)

c) Lower alkoxy group, lower alkoxycarbonyl group, lower alkyl thio group, lower alkyl carbonyl group, lower alkyl carbonyl oxy group or lower alkyl sulphenyl group, lower alkyl sulphonyl group

[each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as for example halogen atom, cyano group, -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra, -SCH<sub>2</sub>Ra (wherein, Ra denotes phenyl group or monocyclic heterocycle group. Phenyl group or  
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monocyclic heterocyclic group may be substituted by 1 or plurality of group selected arbitrarily from group such as for example halogen atom, lower alkyl group, lower haloalkyl group, cyano group, lower alkoxy group, lower haloalkoxy group and the like), lower cycloalkyl group (lower cycloalkyl group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, lower alkyl group, lower haloalkyl group, amino group, hydroxy group, lower alkoxy group and lower haloalkoxy group and the like), lower alkoxy group, lower alkoxy-carbonyl group and lower alkyl thio group and the like).

d) -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra, -SCH<sub>2</sub>Ra

(wherein, Ra has the same aforementioned meaning),

e) alkenyloxy group, alkenyloxy-carbonyl group, alkenyl group, alkenyl-carbonyl oxy group, alkynyl oxy group, alkynyl-oxy-carbonyl group

(each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as for example halogen atom, oxo group, an optionally substituted amino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, acyl oxy group, lower alkyl thio group, carbonyl group, an optionally substituted carbonyl group, lower alkoxy-carbonyl group and the like).

(0018)

In R<sub>3</sub>, R<sub>6</sub>, R<sub>6'</sub> and R<sub>9</sub>, as substituent of "alkenyl group", "alkynyl group", for example halogen atom, cyano group, mercapto group, oxo group, thio group, an optionally substituted amino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, lower alkyl thio group, acyl oxy group, carbonyl group, an optionally substituted carbonyl group, -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra, -SCH<sub>2</sub>Ra (wherein, Ra has the same aforementioned meaning) are nominated.

(0019)

In R<sub>3</sub>, R<sub>6</sub>, R<sub>6'</sub> and R<sub>9</sub>, as substituent of "cycloalkyl group", for example halogen atom, cyano group, mercapto group, oxo group, thio group, lower alkyl group, lower haloalkyl group, an optionally substituted amino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, lower alkyl thio group, acyl oxy group, lower alkyl thio group, carbonyl group, an optionally substituted carbonyl group, lower alkoxy-carbonyl group and the like are nominated.

(0020)

In R<sub>3</sub>, R<sub>6</sub>, R<sub>6'</sub> and R<sub>9</sub>, arbitrary group including in each group from the following a) to c) are nominated as substituent of "aryl group", "saturated or unsaturated heterocyclic group", and said groups may be arbitrarily substituted by 1 or plurality of these.

a) Halogen atom, nitro group, cyano group, mercapto group, an optionally substituted amino group, *© Rising Sun Communications Ltd.*  
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group, an optionally substituted guanidino group, an optionally substituted amidino group, hydroxy group, oxo group, thioxo group, an optionally substituted carbamoyl group, sulpho group, an optionally substituted sulphamoyl group, methylenedioxy group, ethylenedioxy group, b) -Ra, -ORa, -CO<sub>2</sub>Ra, -SO<sub>3</sub>Ra, -SRa, -OCH<sub>2</sub>Ra (wherein, Ra has the same aforesaid meaning).

**(0021)**

c) Lower alkyl group, lower alkoxy group, lower alkoxycarbonyl group, lower alkyl thio group, lower alkyl carbonyl group, lower alkyl carbonyl oxy group, lower alkyl sulphonyl group [each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group for example halogen atom, cyano group, mercapto group, an optionally substituted amino group, hydroxy group, acyl group, acyl oxy group, carboxy-group, an optionally substituted carbamoyl group, an optionally substituted carbamoyloxy group, sulpho group, an optionally substituted sulphamoyl group, -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra, -SCH<sub>2</sub>Ra (wherein, Ra has the same aforesaid meaning), lower cycloalkyl group (lower cycloalkyl group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, lower alkyl group, lower haloalkyl group, an optionally substituted amino group, hydroxy group, lower alkoxy group and lower haloalkoxy group and the like), lower alkoxy group, lower alkoxycarbonyl group and lower alkyl thio group, or the like],

d) Alkenyl group

[alkenyl group may be substituted by 1 or more groups selected arbitrarily from group for example halogen atom, cyano group, mercapto group, oxo group, thioxo group, an optionally substituted amino group, an optionally substituted guanidino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, lower alkoxycarbonyl group, lower alkyl thio group, acyl group, acyl oxy group, carboxy-group, an optionally substituted carbamoyl group, -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra and -SCH<sub>2</sub>Ra (wherein, Ra has the same aforesaid meaning) or the like],

e) Alkynyl group

[alkynyl group may be substituted by 1 or more groups selected arbitrarily from group for example, halogen atom, nitro group, cyano group, mercapto group, oxo group, thioxo group, an optionally substituted amino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, lower alkoxycarbonyl group, lower alkyl thio group, acyl group, acyl oxy group, carboxy-group, an optionally substituted carbamoyl group, -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra and -SCH<sub>2</sub>Ra (wherein, Ra has the same aforesaid meaning) or the like].

**(0022)**

f) Alkenyloxy group, alkenyloxy carbonyl group, alkenyl carbonyl group, alkenyl carbonyl oxy group, alkynyl oxy group, alkynyl oxycarbonyl group

[each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group for example halogen atom, oxo group, an optionally substituted amino group, hydroxy group]

group, lower alkoxy group, lower haloalkoxy group, acyl group, acyl oxy group, lower alkyl thio group, carboxy-group, an optionally substituted carbamoyl group, lower alkoxycarbonyl group and phenyl group and the like],

g) Lower cycloalkyl group, lower cycloalkyl oxy group, lower cycloalkyl carbonyl group, lower cycloalkyl carbonyl oxy group, lower cycloalkyl oxycarbonyl group, lower cycloalkenyl group, lower cycloalkenyl oxy group, lower cycloalkenyl carbonyl group, lower cycloalkenyl carbonyl oxy group, lower cycloalkenyl oxycarbonyl group

[each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as for example halogen atom, nitro group, cyano group, mercapto group, oxo group, thioxo group, lower alkyl group, lower haloalkyl group, an optionally substituted amino group, hydroxy group, lower alkoxy group, lower haloalkoxy group, acyl group, acyl oxy group, lower alkyl thio group, carboxy-group, an optionally substituted carbamoyl group and lower alkoxycarbonyl group and the like].

(0023)

As acyl group, for example, acyl groups represented by following a) or b) are nominated.

a) Lower alkyl carbonyl group or lower alkyl sulphonyl group

[each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, cyano group, -Ra, -ORa, -SRa, -OCH<sub>2</sub>Ra, -SCH<sub>2</sub>Ra (wherein, Ra has the same said meanings), lower cycloalkyl group (lower cycloalkyl group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, lower alkyl group, lower haloalkyl group, amino group, hydroxy group, lower alkoxy group and lower haloalkoxy group and the like), lower alkoxy group, lower alkoxycarbonyl group and lower alkyl thio group and the like]

b) Carbonyl group or the sulphonyl group in which any of cycloalkyl group, aryl group or heterocyclic group is respectively bonded

[each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, cyano group, carboxyl group, lower alkyl group, lower haloalkyl group, lower alkoxy group, lower haloalkoxy group, lower alkyl carbonyl group, lower alkyl carbonyl oxy group or lower alkoxycarbonyl and the like],

as acyl group, in an embodiment, formyl, acetyl, propanoyl, 2-propanoyl, pivaloyl, valeryl, pivaloyl, trifluoroacetyl, benzoyl, naphthoyl, nicotinoyl, methanesulphonyl, trifluoromethane sulfonyl, p-toluenesulfonyl and the like are nominated. Moreover, as far as acyl oxy group is concerned, acyl group-bonded oxy group is stated.

(0024)

As far as substituent of "substituted carbamoyl group", "substituted sulphamoyl group" and  
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"substituted ureide group" are concerned, lower alkyl group, lower haloalkyl group, lower alkoxy group, lower haloalkoxy group or the like are nominated and the same or different plurality of groups may be independently substituted. In an embodiment, as substituted carbamoyl group, diethylcarbamoyl, dimethylcarbamoyl and the like are nominated. As substituted sulphamoyl group, in an embodiment, ethyl sulphamoyl, dimethyl sulphamoyl and the like are nominated. As substituted ureide group, 3-methyl ureide group or the like is nominated.

## (0025)

As far as substituent "substituted amino group" or "substituted guanidino group" is concerned, for example acyl group represented by a) to c) is nominated, and the same or different plurality of groups may be independently substituted.

a) Acyl group,

b) Alkyl group, alkoxycarbonyl group

[each group of this group may be substituted by 1 or plurality of groups arbitrarily selected from group such as halogen atom, cyano group, -Ra (wherein, Ra has the same said meanings), lower cycloalkyl group (lower cycloalkyl group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, lower alkyl group, lower haloalkyl group, amino group, hydroxy group, lower alkoxy group and lower haloalkoxy group and the like), lower alkoxy group, lower alkoxycarbonyl group and lower alkyl thio group and the like],

c) Cycloalkyl group, aryl group or heterocyclic group

[each group of this group may be substituted by 1 or plurality of group selected arbitrarily from group such as halogen atom, cyano group, lower alkyl group, lower haloalkyl group, lower alkoxy group, lower haloalkoxy group and the like],

as embodying substituted amino group, acetamide, propionamide, butylamino, 2-butylamino, methylamino, 2-methyl-1-propylamino, diethylamino and the like are nominated.

## (0026)

As ideal Y, following a) to e) are nominated.

a) -NR<sub>10</sub>CO-R<sub>11</sub>

[R<sub>10</sub> is a lower alkyl group, lower alkenyl group, and R<sub>11</sub> is a lower alkyl group, lower alkyl group which may be substituted by halogen atom, amino group, carboxyl group or hydroxy group, aryl group which may be substituted by lower alkyl group, lower haloalkyl group, lower haloalkoxy group, nitro group, cyano group, hydroxy group, lower alkoxy group, methylenedioxy group or ethylenedioxy group],

b) -NR<sub>10</sub>-D'-E-F-R<sub>12</sub>

[R<sub>10</sub>, E and F have the same aforesaid meanings. D' is -C(=O) or -S(=O)<sub>2</sub>. R<sub>12</sub> is a lower alkyl  
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group, lower haloalkyl group, lower alkoxy group, lower haloalkoxy group, lower alkyl group substituted by -Ra, -O-Ra, -CH<sub>2</sub>-Ra (Ra has the same aforesaid meaning), aryl group which may be substituted by lower alkyl group, lower haloalkyl group, lower haloalkoxy group, nitro group, cyano group, hydroxy group, nitro group, cyano group, halogen atom, lower alkoxy group, methylenedioxy group or ethylenedioxy group, and the saturated heterocycles in which nitrogen atom may be substituted by acyl group],

c) -NR<sub>10</sub>-C(=O)-CHR<sub>13</sub>-NR<sub>14</sub>-R<sub>15</sub>

[R<sub>10</sub> has the same aforesaid meaning. R<sub>14</sub> and R<sub>15</sub> is the same or different and respectively denote hydrogen atom, methyl group, ethyl group. Or R<sub>14</sub> and R<sub>15</sub> are bonded and denote the heterocycle which may be substituted by oxo group. R<sub>13</sub> is lower alkyl group which may be substituted by following groups: carboxyl group, hydroxy group, sulpho group, an optionally substituted amino group, an optionally substituted ureide group, an optionally substituted guanidino group, an optionally substituted lower alkoxycarbonyl group, an optionally substituted lower alkoxy group, an optionally substituted lower thioxy group, an optionally substituted lower alkyl sulphonyl group, an optionally substituted lower alkyl sulphenyl group, saturated or unsaturated heterocycle],

d) -NR<sub>10</sub>-C(=O)-CHR<sub>13</sub>-NR<sub>14</sub>-D"-R<sub>12</sub>

[R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub> and R<sub>14</sub> have the same aforesaid meanings. D" is -C(=O)- or -C(=O)-O-],

e) -NR<sub>16</sub>R<sub>17</sub>

[R<sub>16</sub> and R<sub>17</sub>, together with nitrogen atom, form a saturated or unsaturated 5-7 membered heterocycle which may be substituted by hydroxy group or oxo group).

(0027)

#### Isomers

Heterocyclic derivatives represented by formula (I) of this invention are the concept including all geometric isomers, optical isomers, and these can be used in a form of pure isomer or a mixture thereof.

#### Salts

Heterocyclic derivatives of this invention can form pharmaceutically permitted salts. As pharmaceutically permitted salts, acid addition salt and base addition salt are nominated. As acid addition salt, for example inorganic salt such as hydrochloride, hydrobromic acid salt, sulphate, hydroiodic acid salt, nitrate, phosphate or the like, and organic salt such as citrate, oxalate, acetate, formate, propionate, benzoate, trifluoroacetate, maleate, tartrate, methanesulphonate, benzensulphonate or the like are nominated and as base addition salt, inorganic base salt such as sodium salt, potassium salt, calcium salt, magnesium salt, ammonium salt and the like, organic base salt such as triethylammonium salt, triethanol ammonium salt, pyridinium salt, diisopropyl ammonium salt and the like are nominated. Moreover, in this invention, solventate such as

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hydrate of pharmaceutically permitted salt of heterocyclic derivative or the like and crystals in any form are contained.

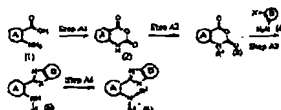
(0028)

A process for the production

Heterocyclic derivative of this invention or isomer thereof can be produced for example by the following process.

**Process for the production A**

Method for the synthesis of heterocyclic derivative represented by general formula (6).



(wherein, A, B, R1, R2 and X have the same aforesaid meanings).

(0029)

Step A1

Step to produce the compound of general formula (2) by reacting the compound of general formula (1) with trichloroacetyl chloride, triphosgene and the like in the presence of base (for example triethylamine and the like) in a suitable solvent. The compound of general formula (2) can be derived by reacting the substance which is equivalent in carbon monoxide as synthon usually at  $-20^{\circ}\text{C}$  to the reflux temperature for 1-48 hours with respect to the compound of general formula (1) in an inert solvent and in accordance with requirements, in the presence of base. Wherein, as inert solvent, a single or mixed solvent of for example, ether species such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent species such as acetonitrile and the like. As base, nitrogen containing organic base species such as triethylamine, diisopropyl ethylamine, tributyl amine, 1,5-diazabicyclo (4.3.0) non-5-ene (DBN), 1,4-diazabicyclo (2.2.2) octane (DABCO), 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU), pyridine, dimethylaminopyridine, picoline and the like, inorganic base species such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate and the like. As substance equivalent to carbon monoxide as synthon, phosgene, diphosgene, triphosgene and dialkyl carbonic acid or the like are nominated. Moreover, the compound represented by general formula (2) is possible to produce by process in accordance with following literature or quoted in the literature (Synthesis, 505 (1980), Advances in Heterocyclic Chemistry, A.R. Katritzky and A.J. Boulton Eds., Academic Press, Vol. 28, 127 (1981)).

(0030)

Step A2

Step to produce the compound of general formula (3) by introducing substituent R1 to nitrogen atom of the compound of general formula (2). Base is caused to act usually at  $-78^{\circ}\text{C}$  to  $50^{\circ}\text{C}$  for 1-48 hours to the commercial compound or the compound of general formula (2) produced by Step A1 in an inert solvent and thereafter halogenated R1 is caused to act usually at  $-78^{\circ}\text{C}$  to  $50^{\circ}\text{C}$  for 1-48 hours, and thereby the compound of general formula (3) can be produced. Wherein, as inert solvent, a single or a mixed solvent of ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, polar organic solvent species such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like. As base, sodium hydride, potassium hydride, lithium hydride, lithium diisopropylamine, lithium bis(trimethylsilyl) amide, potassium t-butoxide, sodium ethoxide and the like are nominated. For example, as halogenated R1, lower alkyl halide such as methyl iodide, ethyl iodide and the like, omega-halogenoester species such as ethyl 1-bromoacetic acid, ethyl 2-bromopropionic acid or the like, omega-halogeno nitriles such as bromo acetonitrile or the like are nominated.

(0031)

Step A3

The compound of general formula (5) can be obtained by carrying out addition condensation reaction of the compound of general formula (3) and the compound of general formula (4) from room temperature to reflux temperature in an inert solvent. Wherein, as inert solvent, a single or a mixed solvent of organic acid such as acetic acid, propionic acid, formic acid or the like are preferred, and single or mixed solvents of polar organic solvent species such as dimethylsulfoxide and the like, hydrocarbons such as toluene, benzene or the like and ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane including mineral acid such as hydrochloric acid, sulphuric acid, hydrogen bromide or the like and organic acid such as acetic acid, formic acid methanesulfonic acid, toluenesulfonic acid or the like, or water are nominated.

(0032)

Step A4

Step to produce the compound of general formula (6) by introducing substituent R2 to amino group of the compound of general formula (5). Below four processes are exemplified. Moreover, in R2, the functional group may be protected in accordance with requirements by protecting group. As protecting group, for example group described in Protective Groups in Organic Synthesis 2nd Edition (T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc) can be used.

**Process 1**

With respect to the compound represented by general formula (5), the reaction is carried out usually at 0°C-50°C for 1-48 hours in the presence or absence of various acyl halide species, sulfonyl halide species, acyl halide amino acid, cyanidation halogen or acid anhydride and solvent, in the presence of base, and in accordance with requirements, using phase transfer catalyst, and thereby substituent R2 is introduced. Wherein, as solvent, there are single or mixed solvents of for example alcohol such as methanol, ethanol, isopropanol, butanol, ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent species such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like. As base, nitrogen containing organic base species such as triethylamine, diisopropyl ethylamine, tributyl amine, 1,5-diazabicyclo (4.3.0) non-5-ene (DBN), 1,4-diazabicyclo (2.2.2) octane (DABCO), 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU), pyridine, dimethylaminopyridine, picoline and the like, inorganic base species such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, sodium hydride or the like, alcoholate species such as potassium t-butoxide, sodium ethoxide and the like are nominated. As phase transfer catalyst, quaternary ammonium salt such as tetrabutylammonium bromide, benzyltriethylammonium bromide and the like, crown ether species such as 18-Crown-6-ether and the like are nominated. Moreover, subsequently to aforesaid reaction (introduction of substituent R2), in accordance with requirements, hydrolysis is carried out using solvent such as alcohol and the like in the presence of base. Usually the reaction is carried out between 0°C and reflux temperature, and as a base, alkali metal carbonate - bicarbonate such as potassium carbonate, sodium carbonate, sodium bicarbonate, potassium hydrogen carbonate and the like, alkaline earth metal hydroxide and alkali metal hydroxide such as magnesium hydroxide, sodium hydroxide, potassium hydroxide and the like, tetrabutyl ammonium fluoride and the like may be used. As solvent, an alcohol such as methanol, ethanol, isopropanol, butanol and the like, water, ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like used for ordinary hydrolysis can be used alone or as a mixed solvent.

(0033)

**Process 2**

A base is added in accordance with requirements to the compound of general formula (5) and carboxylic acid derivative in the presence of condensing agent in an inert solvent, thereafter the reaction is carried out usually at -20°C to room temperature for 1-48 hours and thereby the compound of general formula (6) can be produced. As inert solvent, a single or a mixed solvent of ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like,  
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hydrocarbons such as hexane, heptane, toluene, benzene, xylene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like. The base is not limited in particular so long as it is a base used in ordinary reaction as base, and for example nitrogen containing organic base species such as N-methylmorpholine, triethylamine, diisopropyl ethylamine, tributyl amine, DBU, DBN, DABCO, pyridine, dimethylaminopyridine, picoline and the like, inorganic base species such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, sodium hydride and the like are nominated. As phase transfer catalyst, quaternary ammonium salt such as tetrabutylammonium bromide, benzyltriethylammonium bromide and the like, crown ether species such as 18-Crown-6-ether and the like are nominated. As condensing agent, the species written in Experiment Chemicals Lecture (Nippon Kagakukai, Maruzen) vol. 22 are nominated. For example, phosphoester species such as cyano phosphoric acid diethyl, diphenylphosphoryl azide and the like, carbodiimide species such as 1-ethyl-3 (3-dimethylaminopropyl)-carbodiimide · hydrochloride, dicyclohexylcarbodiimide and the like, combination of disulfide species such as 2,2'-dipyridyl disulphide and the like and phosphine such as triphenylphosphine and the like, phosphorus halides such as N,N'-bis (2-oxo-3-oxazolidinyl) phosphinic chloride, combination of azo dicarboxylic acid diester such as azo dicarboxylic acid diethyl ester and phosphine such as triphenylphosphine and the like, 2-halo-1-lower alkyl pyridinium halides such as 2-chloro-1-methylpyridinium iodide or the like are nominated.

(0034)

**Process 3**

Step to produce the compound represented by general formula (6) by reacting the compound represented by general formula (5) and mixed acid anhydride. In other words, it is a process wherein lower alkoxy or aryloxy carbonyl halide is reacted with respect to the carboxylic acid derivative in the presence of base in an inert solvent usually at -78°C to room temperature, and after arbitrarily time has elapsed, a compound represented by general formula (5) or a compound represented by general formula (5) in an inert solvent is added usually at -78°C to room temperature and thereby the compound represented by general formula (6) is derived. Wherein, as inert solvent, a single or a mixed solvents of ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent species such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like are nominated. As base, there are for example nitrogen containing organic base species such as N-methylmorpholine, triethylamine, diisopropyl ethylamine, tributyl amine, DBU, DBN, DABCO, ©Rising Sun Communications Ltd.

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pyridine, dimethylaminopyridine, picoline and the like, inorganic base species such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate or the like, potassium t-butoxide, or the like.

(0035)

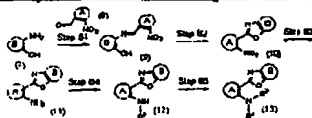
**Process 4**

When substituent R2 is formyl group (CHO group), the compound represented by general formula (6) can be produced using the processes comprising a process via Vilsmeier type intermediate shown in Journal of Organic Chemistry 1311 (1984) and Synlett 659 (1992), a process using a formic acid described in Chemical and Pharmaceutical Bulletin 2892 (1983), a process using a formic acid-acetic acid described in Comprehensive Organic Transformations (R.C. Larock, VCH publishers, inc) and the like. When the substituent R2 of the compound of general formula (6) has protected group, deprotection can be carried out when desired. This deprotection can be performed by general process for example a process described in Protective Groups in Organic Synthesis 2nd Edition (T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc.) may be used. When substituent R2 of the compound of general formula (6) is including primary or secondary amine or hydroxy group, in accordance with process 1 of Step A4, primary or secondary amine or hydroxy group of substituent R2 can be substituted. In this case, when substituent R2 of the compound of general formula (6) has protected group, deprotection can be carried out when desired. This deprotection can be performed by general process, and for example a process described in Protective Groups in Organic Synthesis 2nd Edition (T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc.) may be used.

(0036)

**Process for the production B**

Method for the synthesis of heterocyclic derivative represented by general formula (13).



(wherein, A, B, R1 and R2 have the same aforesaid meanings).

(0037)

**Step B1**

Step to produce the compound of general formula (9) by addition condensation of the compound of general formula (7) and the compound of general formula (8). The compound represented by general formula (7) and the compound represented by general formula (8) are reacted at room temperature to reflux temperature in an inert solvent, and the compound represented by general

formula (9) can be obtained. As inert solvent, for example a single or a mixed solvent of ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as hexane, heptane, toluene, benzene, xylene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, hydrocarbons such as pentane, cyclopentane, hexane, cyclohexane, heptane, cycloheptane, benzene, toluene, xylene or the like, halogen hydrocarbon species such as methylene chloride, chloroform or the like, esters such as ethyl acetate, propyl acetate, ethers such as ether, tetrahydrofuran, dioxane, dimethoxyethane or the like, ketones such as acetone and the like, polar organic solvent such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like are nominated.

(0038)

Step B2

The compound represented by general formula (9) is cyclised by treating in inert solvent at usually -78 to 200°C in the presence of oxidant and is possible to obtain the compound represented by general formula (10). Wherein, as inert solvent, a single or a mixed solvent of for example ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent species such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like are nominated. As oxidant, silver oxide (I), manganese oxide (IV) or the like are nominated. Moreover, this cyclisation can be performed using a process shown in Tetrahedron Letters 2621 (1997), Tetrahedron Letters 8869 (1996), Journal Heterocyclic Chemistry 1539 (1998), Synthetic Communications 1537 (1988), Heterocycles 1279 (1980) or the like.

Step B3

Using a process shown in Comprehensive Organic Transformations (R.C. Larock, VCH publishers, inc.), nitro group of the compound of general formula (10) is reduced, and the compound represented by general formula (II) can be produced.

Step B4

In accordance with Step A4, the substituent R2 of the compound of general formula (11) is introduced into amino group, and the compound represented by general formula (12) can be produced.

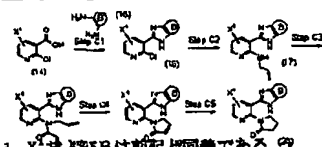
Step B5

In accordance with Step A2, the substituent R1 is introduced into amino group of the compound  
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### Process for the production C

Method for the synthesis of heterocyclic derivative represented by general formula (20).



(0040)

Step to produce the compound of general formula (16) from the compound of general formula (14) and the compound of general formula (15). In inert solvent, the compound represented by general formula (14) and the compound represented by general formula (15) are reacted at usually -20°C to room temperature for 1-48 hours in the presence of condensing agent after the addition of base in accordance with requirements. As inert solvent, a single or a mixed solvent of for example ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as hexane, heptane, toluene, benzene, xylene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, polar organic solvent such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like are nominated. The base is not limited in particular as base so long as it is the base used in ordinary reaction as base, and for example nitrogen containing organic base species such as N-methylmorpholine, triethylamine, diisopropyl ethylamine, tributyl amine, 1,5-diazabicyclo (4.3.0) non-5-ene (DBN), 1,4-diazabicyclo (2.2.2) octane (DABCO), 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU), pyridine, dimethylaminopyridine, picoline and the like, inorganic base species such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, sodium hydride and the like are nominated. As condensing agent, the species described in Experiment Chemicals Chairs vol. 22 (edited by Nippon Kagaku Kai, Maruzen) are nominated. For example, phosphoester species such as cyano phosphoric acid diethyl, diphenylphosphoryl azide and the like, carbodiimide species such as 1-ethyl-3 (3-dimethylaminopropyl)-carbodiimide • hydrochloride, dicyclohexylcarbodiimide and the like, combination of a disulfide species such as 2,2'-dipyridyl disulphide and phosphine such as triphenylphosphine and the like, phosphorus halides such as N,N'-bis (2-oxo-3-oxazolidinyl) phosphonic chloride, a combination of azo dicarboxylic acid diester such as azo dicarboxylic acid diethyl ester and phosphine such as triphenylphosphine and the like, 2-halo-1-lower alkyl

pyridinium halides such as 2-chloro-1-methylpyridinium iodide or the like are nominated. Thereafter, in the same way as in Step A3, the product obtained by aforesaid process can be derived to the compound represented by general formula (16).

(0041)

Step 2C

The compound of general formula (16) and allylamine are caused to react usually at room temperature to 120°C in a sealed reaction container in the presence or absence of inert solvent, and thereby the compound of general formula (17) can be obtained. Wherein, as inert solvent, a single or a mixed solvent of hydrocarbons such as benzene, toluene, xylene and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, polar organic solvent species such as dimethylsulfoxide and the like, water or the like are nominated.

(0042)

Step 3C

Crotonyl group are introduced by carrying out the reaction with respect to the compound represented by general formula (17) usually at 0°C-50°C in the presence of base for 1-48 hours in the presence or absence of an inert solvent and trans-crotonyl chloride, and the compound represented by general formula (18) can be produced. Wherein, as inert solvent, a single or a mixed solvent of ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent species such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like are nominated. As base, for example nitrogen containing organic base species such as triethylamine, diisopropyl ethylamine, tributyl amine, 1,5-diazabicyclo (4.3.0) non-5-ene (DBN), 1,4-diazabicyclo (2.2.2) octane (DABCO), 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU), pyridine, dimethylaminopyridine, picoline and the like, inorganic base species such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, sodium hydride, or the like, alcoholate species or the like such as potassium t-butoxide, sodium ethoxide and the like.

Step 4C

Cyclisation reaction of the compound of general formula (18) is carried out using processes shown in Chemical Review 2963 (2000), Tetrahedron 4413 (1998), Angewandte Chemie, International Edition in English 2036 (1997), Journal of the Chemical Society: Perkin Transactions I 371 (1998) and the like, and the compound of general formula (19) can be produced.

(0043)

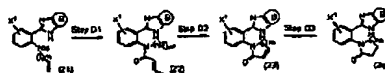
Step 5C

1,4-reductive reaction is carried out by the reaction with respect to the compound of general formula (19) in the presence of a reducing agent and an inert solvent usually at 0°C-50°C for 1-48 hours, and the compound represented by general formula (20) can be produced. Wherein, as reducing agent, sodium borohydride, hydrogenated boron potassium, hydrogenated boron bis (triphenylphosphine) copper (I), hydrogenated tri-sec-butyl boron sodium, hydrogenated tri-sec-butyl boron potassium, hydrogenated tri-sec-butyl boron lithium or the like are nominated. As inert solvent, a single or a mixed solvent of alcohol such as methanol, ethanol, isopropanol or the like, ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like, ketones such as acetone and the like, polar organic solvent species such as acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, hexamethylene phospho amide and the like are nominated.

(0044)

**Process for the production D**

Method for the synthesis of heterocyclic derivative represented by general formula (24).



(wherein, X1 and B have the same aforesaid meanings. m denotes 1 or 2).

Step D1

In accordance with Step C3, the compound of general formula (22) can be produced.

Step D2

In accordance with Step C4, the compound of general formula (23) can be produced.

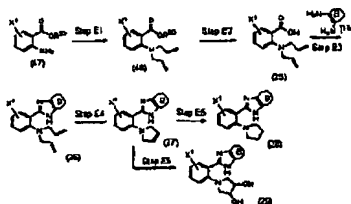
Step D3

In accordance with Step C5, the compound of general formula (24) can be produced.

(0045)

**Process for the production E**

Method for the synthesis of heterocyclic derivative of general formula (28) and general formula (29).



(wherein, X1 has the same aforesaid meaning. R20 denotes a lower alkyl group).

#### Step E1

In accordance with Step A2, the compound of general formula (48) can be synthesised from the compound of general formula (47).

#### Step E2

The compound of general formula (48) is reacted at room temperature to reflux temperature in the presence of base in a solvent for 1-48 hours, and the compound of general formula (25) can be obtained. Wherein, as solvent, an alcohol such as methanol, ethanol, isopropanol, butanol and the like, water, ethers such as tetrahydrofuran, dioxane and the like can be used as a single species or as a mixed solvent. As base, inorganic base such as sodium bicarbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide and the like are nominated.

#### Step E3

In accordance with Step C1, the compound of general formula (25) can be produced.

#### Step E4

In accordance with Step C4, the compound of general formula (27) can be produced.

#### Step E5

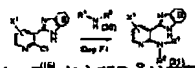
The compound of general formula (28) can be produced by reacting with respect to the compound represented by general formula (27) under hydrogen atmosphere usually at 0°C-50°C, 1-10 atmosphere for 1-48 hours in the presence of catalyst and inert solvent. Wherein, as catalyst, palladium carbon, palladium black, Raney nickel, platinum oxide, platinum black, rhodium-alumina, triphenyl phosphine-rhodium chloride, palladium-barium sulphate or the like are nominated. As inert solvent, a single or a mixed solvent of alcohol such as methanol, ethanol, isopropanol or the like, ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane and the like are nominated.

**Step E6**

The compound represented by general formula (29) can be produced by carrying out the oxidation reaction from the compound represented by general formula (27). As for this oxidation reaction, processes shown in comprehensive organic transformations (R.C. Larock, VCH publishers, inc.) can be used and thereby the compound represented by general formula (29) can be produced.

**(0046)****Process for the production F**

Method for the synthesis of heterocyclic derivative represented by general formula (31).



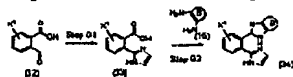
(wherein, X1, B, R1 and R2 have the same aforesaid meanings).

**Step F1**

In accordance with Step C2, the compound of general formula (31) can be produced.

**(0047)****Process for the production G**

Method for the synthesis of the compound represented by general formula (34).



(wherein, X1 and B have the same aforesaid meanings).

**Step G1**

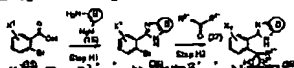
Cyclisation reaction of the compound represented by general formula (32) is carried out using a process described in Journal of the American Chemical Society 5500 (1978), and the compound represented by general formula (33) can be produced.

**Step G2**

In the same way as in desired step of Step C1, the compound represented by general formula (34) can be produced from the compound represented by general formula (33) and the compound represented by general formula (15).

**(0048)****Process for the production H**

Method for the synthesis of the compound represented by general formula (38).



(wherein, X1, B, R1' and R2' have the same aforesaid meanings).

#### Step H1

In the same way as in desired step of Step C1, the compound represented by general formula (36) can be produced from the compound represented by general formula (35) and the compound represented by general formula (15).

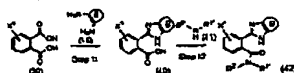
#### Step H2

The reaction is carried out with respect to the compound represented by general formula (36) usually at  $-100^{\circ}\text{C}$  to  $0^{\circ}\text{C}$  for 1-2 hours in the presence of an alkyllithium and an inert solvent, and continuing it is reacted with the compound represented by general formula (37) usually for 1-5 hours, and the compound represented by general formula (38) can be produced. Wherein, as alkyllithium, n-butyllithium, sec-butyllithium, tert-butyllithium or the like are nominated. As inert solvent, a single or a mixed solvent of ethers such as tetrahydrofuran, diethyl ether, dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as toluene, benzene or the like are nominated.

(0049)

#### Process for the production I

Method for the synthesis of the compound represented by general formula (42).



(wherein, X1, B, R1' and R2' have the same aforesaid meanings).

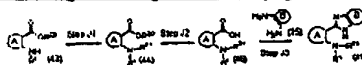
#### Step I1

In accordance with Step C1, the compound represented by general formula (40) can be produced from the compound represented by general formula (39) and the compound represented by general formula (15).

#### Step I2

The compound represented by general formula (42) can be produced from the compound represented by general formula (40) and compound represented by general formula (41) in accordance with step to form amide bond using condensing agent demonstrated in Step C1.

(0050)

**Process for the production J****Method for the synthesis of the compound represented by general formula (46)**

(wherein, A, B, R1 and R20 have the same aforesaid meanings. Or R21 denotes a lower alkyl group and lower alkylene group).

**Step J1**

In accordance with Step A2, the compound of general formula (44) can be synthesised.

**Step J2**

In accordance with Step E2, the compound of general formula (45) can be synthesised.

**Step J3**

In accordance with Step C1, the compound of general formula (46) can be synthesised.

(0051)

**Drug applications**

Heterocyclic derivatives of this invention have osteoclast differentiation induction inhibitory action and/or bone destruction inhibitory action, and are useful as anti-inflammatory agent and antirheumatic. Moreover, the compounds of this invention are also useful for therapy of diseases accompanied by bone regeneration insufficiency. In an embodiment, it can be applied for therapy of osteoporosis, periodontal disease, bone destruction due to cancer of bone metastasis, hypercalcemia, skewness of articulation with prosthesis replacement.

(0052)

**Preparation**

Heterocyclic derivative of this invention or a pharmacologically acceptable salt thereof can be in various kinds of formulations (for example liquid agent, solid agent, encapsulated formulation or the like). As composition for oral administration, for example tablet, encapsulated formulation, pills, granule, powder, liquid agent, suspending agent or the like are nominated, and as composition for parenteral administration, for example aqueous agent for injection or oily agent, ointment, cream agent, lotion agent, aerosol, suppository, patch or the like are nominated. In general it is formed to orally administered agent, injection, inhalant or suppository with compound which is effective ingredient itself or together with conventionally used carrier. For example, as orally administered agent, it is pharmaceutically formulated into a formulation such as tablet, granules, fine granules, powder, soft or hard capsule agent, liquid agent, emulsion,

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suspending agent, syrup or the like, and these preparations can be prepared in accordance with conventional methods of pharmaceutical formulation. Injection can be prepared using conventional methods, and for example, the aforesaid compound is dissolved in an appropriate solvent (for example, sterilized water, buffer, physiological saline and the like) thereafter, sterilised by filtration with a filter and the like, and thereafter, packed in a sterile container, and thereby the formulation can be produced. A suppository can be prepared by conventional method for the preparation using conventionally used base (for example cacao butter, lauric fat, glycerogelatin, macrogol, Witepsol and the like). An inhalant can be prepared in accordance with usual practice means for preparation. The content of aforesaid compound in the formulation can be suitably adjusted depending on the formulation, application disease or the like. When a liquid preparation is formed, it is desirable to store by cryopreservation or by elimination of water content using lyophilisation or the like. Lyophilisation preparation is used by redissolving at the time of use by adding distilled water for injection or the like.

**(0053)**

Aforesaid preparations are prepared using techniques familiar to the prior art, and non-toxic and also inert carriers or excipients which are conventionally used in pharmaceutical preparation sphere may be included. Moreover, stabilising agent (albumin, globulin, gelatine, glycine, mannitol, glucose, dextran, sorbitol, ethylene glycol and the like), solubiliser, antioxidant, analgesic, isotonicising agent or the like may be included.

**(0054)****Administration method**

The dose changes depending on the condition of patient such as age, body weight or the like, symptoms, administration route. However, as the effective ingredient quantity of the compounds of this invention, it is usually 0.05-5000 mg, preferably 0.5-500 mg as daily administered dose per adult, and this can be continuously administered 1-3 times daily, or discontinuous administration or intermittent administration method can be carried out.

**(0055)****Examples**

Below the compounds of this invention and processes for the production thereof are described using Examples. Wherein these are just for illustrations, and this invention is not limited only to these. In Examples, the meanings of abbreviations to be used are as follows.

THF: tetrahydrofuran

Boc: t-butoxycarbonyl.



(0056)

## Example 1

N-[2-(1H-benzimidazol-2-yl)-4-bromo phenyl]-N-methylacetamide.

Acetyl chloride (801  $\mu$ l) was added dropwise to pyridine (25 ml) solution of 2-(1H-benzimidazol-2-yl)-4-bromo-N-methylaniline (2.27 g) cooled to 5°C and was reacted at 25°C for 48 hours. The reaction mixture was transferred to 2 N HCl aqueous solution (400 ml), and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in isopropanol (3 ml) and potassium carbonate (464 mg) was added to this solution and was reacted for 12 hours. The reaction mixture was transferred to water (30 ml) and extraction was carried out with ethyl acetate (10 ml x 2). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. Crystallisation of residue was carried out with ethyl acetate-hexane. Thereby, the title compound (1.58 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  1.65 (s, 3H), 3.01 (s, 3H), 7.20-7.27 (m, 2H), 7.49 (d, J = 8.5 Hz, 1H), 7.57-7.67 (m, 2H), 7.80 (dd, J = 2.3, 8.5 Hz, 1H), 8.18 (d, J = 2.3 Hz, 1H)

MS (EI): 343 (M<sup>+</sup>, 61 %).

Anal, Calcd for C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O: C, 55.83; H, 4.10; N, 12.21.

Found: C, 55.79; H, 4.42; N, 11.88.

(0057)

## Example 2

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N, 2-dimethylpropan amide.

At 25°C, isobutyryl chloride was added dropwise (100  $\mu$ l) with respect to pyridine (3 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (290 mg). It was stirred for 14 hours, and thereafter it was discharged in water (60 ml), and it was extracted with ethyl acetate (30 ml x 3). The organic layer was dried with sodium sulphate, and was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1) and a white oily substance was obtained. Potassium carbonate (1.38 g) and isopropanol (10 ml) were added to this, and it was stirred under a nitrogen atmosphere at room temperature for 36 hours. Potassium carbonate was removed by recovering by filtration, and the filtrate was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1) and the title compound (125 mg) was obtained as a white solid.

mp: 284-285°C

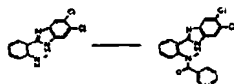
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.58 (d,  $J = 6.7$  Hz, 3H), 0.84 (d,  $J = 6.7$  Hz, 3H), 2.24 (m, 1H), 3.10 (s, 3H), 7.53-7.96 (m, 6H), 13.05 (br, 1H).

IR (KBr): 1628, 1448, 1377, 1288, 1115, 1094  $\text{cm}^{-1}$ .

(0058)

**Example 3**

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylnicotin amide.



At 25°C, nicotinoyl chloride hydrochloride (231 mg) was added with respect to pyridine (5 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (290 mg). The mixture was stirred for 12 hours, and thereafter it was discharged into saturated aqueous sodium bicarbonate (60 ml) and was extracted with ethyl acetate (30 ml x 3). The organic layer was washed with water (50 ml x 2) and next was dried with sodium sulphate, and concentrated under reduced pressure. The residue was refined by silica gel column chromatography (ethyl acetate) and the title compound (150 mg) was obtained as a white solid.

mp: 236-237°C

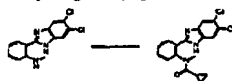
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  3.30 (s, 3H), 7.07-7.12 (m, 1H), 7.28-7.32 (m, 1H), 42-8.10 (m, 7H), 8.35 (d,  $J = 3.1$  Hz, 1H), 12.90 (br, 1H).

IR (KBr): 1611, 1446, 1382, 1300, 1098  $\text{cm}^{-1}$ .

(0059)

**Example 4**

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylcyclopropane carboxamide.



At 10°C, cyclopropane carbonyl chloride (0.11 ml) was added dropwise to pyridine (4 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (290 mg). It was stirred for 12 hours, and thereafter it was discharged into saturated aqueous sodium bicarbonate (60 ml) and was extracted with ethyl acetate (30 ml x 3). The organic layer was washed with water (50 ml x 2) and next dried with sodium sulphate, and concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1) and a white oily substance was obtained. To this, potassium carbonate (1.38 g) and isopropanol (10 ml) were added, and it was stirred under a nitrogen atmosphere at room temperature for 12 hours. Potassium carbonate was removed by recovering by filtration, and the filtrate was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane /

ethyl acetate = 1/1) and the title compound (60 mg) was obtained as a white solid.

mp: 243-244.5°C

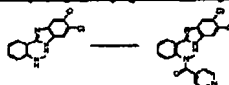
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.12-0.25 (m, 3H), 0.40-0.46 (m, 1H), 0.59-0.63 (m, 1H), 3.18 (s, 3H), 7.55-7.98 (m, 6H), 12.92 (br, 1H).

IR (KBr): 1625, 1446, 1379, 1294, 1118, 773 cm<sup>-1</sup>.

(0060)

**Example 5**

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methyl isonicotin amide.



At 25°C, isonicotinoyl chloride hydrochloride (231 mg) was added with respect to pyridine (5 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (290 mg). The mixture was stirred overnight, and thereafter it was discharged into saturated aqueous sodium bicarbonate (60 ml), and it was extracted with ethyl acetate (30 ml x 3), dried with sodium sulphate, and concentration was carried out under reduced pressure. The residue was refined by silica gel column chromatography (ethyl acetate) and the title compound (280 mg) was obtained as a white solid.

mp: 262-263°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.29 (s, 3H), 6.86 (d, J = 1.7 Hz, 2H), 7.42-7.98 (m, 6H), 29 (d, J = 1.7 Hz, 2H), 12.96 (br, 1H).

IR (KBr): 1618, 1594, 1447, 1381, 1300, 1100 cm<sup>-1</sup>.

(0061)

**Example 6**

N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methoxyphenyl]-N-methylacetamide.



At 25°C, acetyl chloride (0.4 ml) was added dropwise with respect to pyridine (5 ml) solution of 2-(5-chloro-1H-imidazol-2-yl)-4-methoxy-N-methylaniline (540 mg). It was stirred for two hours, and thereafter it was discharged into saturated aqueous sodium chloride solution (60 ml) and was extracted with ethyl acetate (80 ml x 3). The organic layer was washed with water (100 ml x 2) and next was dried with sodium sulphate, and concentrated under reduced pressure. To the residue, potassium carbonate (2.6 g) and isopropanol (20 ml) were added and stirred under a nitrogen atmosphere at 60°C for eight hours. Potassium carbonate was removed by recovering by filtration, and the filtrate was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/2) and white solid was obtained. This solid was washed with hexane and the title compound (350 mg) was obtained.

Mp: 173-178°C (dec)

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.63 (s, 3H), 3.00 (s, 3H), 3.88 (s, 3H), 7.17 (dd, J = 2.9, 8.8 Hz, 1H), 7.24 (dd, J = 2.2, 8.6 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 2.9 Hz, 1H), 7.59-7.65 (m, 2H), 12.87 (br, 1H).

IR (KBr): 1363, 1504, 1439, 1385, 1320, 973 cm<sup>-1</sup>.

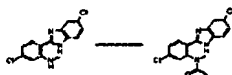
Anal, Calcd for C<sub>17</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 61.92; H, 4.89; N, 12.74.

Found: C, 61.55; H, 4.88; N, 12.59.

(0062)

Example 7

N-[5-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



At 10°C, acetyl chloride (1.46 ml) was added dropwise with respect to pyridine (15 ml) solution of 5-chloro-2-(6-chloro-1H-imidazol-2-yl)-N-methylaniline (2.0 g). It was stirred for one hour 30 minutes, and thereafter it was discharged into saturated aqueous sodium chloride solution (100 ml) and was extracted with ethyl acetate (80 ml x 3). The organic layer was washed with saturated aqueous sodium chloride solution (100 ml x 2) and next was dried with sodium sulphate, and concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/2) and straw-coloured liquid was obtained. To this, potassium carbonate (6.9 g) and isopropanol (50 ml) were added, and it was stirred under a nitrogen atmosphere at room temperature for two days. Potassium carbonate was removed by recovering by filtration, and the filtrate was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1) and white solid was obtained. This solid was washed with hexane and the title compound (1.66 g) was obtained.

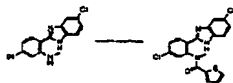
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.66+2.05 (s, 3H), 3.02+3.30 (s, 3H), 7.19-7.29 (m, 1H), 7.56-7.75 (m, 4H), 7.91-7.98 (m, 1H).

IR (KBr): 1658, 1423, 1372, 1062, 925 cm<sup>-1</sup>.

(0063)

Example 8

Synthesis of N-[5-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-thiophene carboxamide.



At 10°C, with respect to mixed solution of 5-chloro-2-(6-chloro-1H-imidazol-2-yl)-N-methylaniline (800 mg), triethylamine (0.76 ml), dichloromethane (30 ml) and tetrahydrofuran

(20 ml) was added dropwise 2-thiophenecarbonyl chloride (0.29 ml). It was stirred for 15 minutes, and thereafter it was discharged into saturated aqueous sodium chloride solution (100 ml) and was extracted with ethyl acetate (80 ml x 3). The organic layer was dried with sodium sulphate, and thereafter concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/2 to 2/1) and the title compound (0.43 g) was obtained as a white solid.

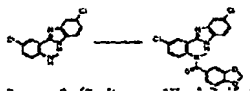
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.34 (s, 3H), 6.65 (m, 1H), 6.83 (m, 1H), 7.21 (m, 1H), 7.49-7.78 (m, 5H), 7.98 (d, J = 8.4 Hz, 1H).

IR (KBr): 1609, 1566, 1416, 1365, 1296, 1103 cm<sup>-1</sup>.

(0064)

#### Example 9

Synthesis of N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)phenyl]-N-methyl-1,3-benzodioxol-5-carboxamide.



At 10°C, with respect to 4-chloro-2-(5-chloro-1H-imidazol-2-yl)-N-methylaniline (1.5 g), triethylamine (2.2 ml) and dichloromethane (30 ml) solution was added dropwise the mixed solution of piperonyl chloride (976 mg), pyridine (5 ml) and dichloromethane (30 ml). It was stirred for three hours, and thereafter it was discharged into liquid a mixture of saturated aqueous sodium chloride solution (80 ml) and saturated aqueous sodium bicarbonate (80 ml), and it was extracted with ethyl acetate (100 ml x 3). The organic layer was dried with sodium sulphate and concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 3/1) and straw-coloured liquid was obtained. To this, potassium carbonate (6.9 g) and isopropanol (80 ml) were added, and it was stirred under a nitrogen atmosphere at room temperature for two days. Potassium carbonate was removed by recovering by filtration, and the filtrate was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 3/2) and the title compound (1.82 g) was obtained as a white solid.

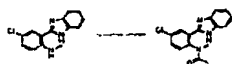
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.20 (s, 3H), 5.93 (s, 2H), 6.49-6.61 (m, 3H), 7.26 (m, 1H), 7.34-7.74 (m, 4H), 7.86 (m, 1H).

IR (KBr): 1589, 1486, 1395, 1248, 1106, 1037 cm<sup>-1</sup>.

(0065)

#### Example 10

N-[2-(1H-benzimidazol-2-yl)-4-chlorophenyl]-N-methylacetamide.



Acetyl chloride (316  $\mu$ l) was added to pyridine (20 ml) solution of 2-(1H-benzimidazol-2-yl)-4-chloro-N-methylaniline (750 mg) at 25°C, and it was reacted for ten minutes. The reaction mixture was transferred to water (200 ml) and extraction was carried out with ethyl acetate (80 ml x 3). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The obtained white solid was recrystallised using ether / hexane, and the title compound (364 mg) was obtained.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  3.01 (s, 3H), 3.32 (s, 3H), 7.21-7.26 (m, 2H), 7.53-7.69 (m, 4H), 8.05 (d,  $J = 2.6$  Hz, 1H), 12.79 (bs, 1H)

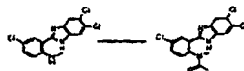
MS (EI): 299 ( $M^+$ , 39 %).

HRMS (EI): calcd for  $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{O}$  299.0825, Found 299.0804.

(0066)

#### Example 11

N-[4-chloro-2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



Acetyl chloride (208  $\mu$ l) was added to pyridine (20 ml) solution of 4-chloro-2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (870 mg) at 25°C, and it was reacted for 30 minutes. The reaction mixture was transferred to water (200 ml), and extraction was carried out with ethyl acetate (80 ml x 3). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The obtained white solid was recrystallised using ether and the title compound (348 mg) was obtained.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.99 (s, 3H), 3.31 (s, 3H), 7.58 (d,  $J = 8.5$  Hz, 1H), 7.71 (dd,  $J = 2.5$ , 8.5 Hz, 1H), 7.88 (s, 2H), 8.06 (d,  $J = 2.5$  Hz, 1H)

MS (EI): 367 ( $M^+$ , 23 %).

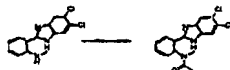
Anal, Calcd for  $\text{C}_{16}\text{H}_{12}\text{Cl}_3\text{N}_3\text{O}$ : C, 52.13; H, 3.28; N, 11.40.

Found: C, 51.89; H, 3.00; N, 11.00.

(0067)

#### Example 12

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



Acetyl chloride (551  $\mu$ l) was added to pyridine (30 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (2.06 g) at 25°C, and it was reacted for one hour. The reaction mixture

was transferred to water (300 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (630 mg) was obtained as yellow solid.

mp: 158-161°C

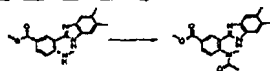
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.63 (s, 3H), 3.01 (s, 3H), 7.50-7.54 (m, 1H), 7.56-7.68 (m, 2H), 7.85 (s, 2H), 7.92-7.95 (m, 1H), 12.98 (br, 1H)

MS (EI): 333 (M<sup>+</sup>, 95 %).

(0068)

**Example 13**

Methyl 4-[acetyl (methyl) aminol-3-(5,6-dimethyl-1H-benzimidazol-2-yl)] benzoate.



At 25°C, acetyl chloride (527 μl) was added dropwise to pyridine (25 ml) solution of methyl 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-(methylanilino) benzoate (2.55 g) and dimethylaminopyridine (302 mg) and it was reacted for two days. The reaction mixture was transferred to 2N HCl aqueous solution (200 ml) and extraction was carried out with ethyl acetate (80 ml x 2). The organic layer was dried with magnesium sulphate, and, after filtration, it was left to stand overnight. Precipitated white solid was separated by filtration and was washed with hexane and thereafter, dried. Thereby, the title compound (1.21 g) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.64 (s, 3H), 2.32 (s, 3H), 2.34 (s, 3H), 3.02 (s, 3H), 3.92 (s, 3H), 7.38-7.42 (m, 2H), 7.63-7.66 (m, 1H), 8.08-8.12 (m, 1H), 8.50-8.51 (m, 1H)

MS (EI): 351 (M<sup>+</sup>, 60 %).

HRMS(EI): calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>, 351.1583, Found 351.1580.

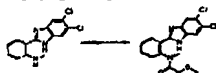
Anal, Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>·0.2H<sub>2</sub>O: C, 67.66; H, 6.08; N, 11.83.

Found: C, 67.50; H, 6.01; N, 11.68.

(0069)

**Example 14**

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-2-methoxy-N-methylacetamide.



At 25°C, methoxyacetyl chloride (792 μl) was added dropwise to pyridine (50 ml) solution of 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (2.11 g) and it was reacted for one hour. The reaction mixture was transferred to 1N-HCl aqueous solution (300 ml), and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it

was filtered, and thereafter it was concentrated under reduced pressure. The obtained yellow solid was washed with ether and was dried under reduced pressure. Thereby, the title compound (598 mg) was obtained.

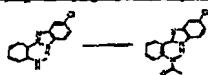
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  3.02 (s, 3H), 3.06 (s, 3H), 3.59 (d,  $J = 14.8$  Hz, 1H), 3.73 (d,  $J = 14.8$  Hz, 1H), 7.50-7.70 (m, 3H), 7.83-8.03 (m, 3H)

MS (EI): 363 ( $M +$ , 1 %).

(0070)

**Example 15**

N-[2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



At  $10^\circ\text{C}$ , acetyl chloride (2.0 ml) was added dropwise to pyridine (35 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (3.28 g) and it was reacted for one hour. The reaction mixture was transferred to 1N HCl aqueous solution (200 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in isopropanol (150 ml) and potassium carbonate (20.38 g) was added and was reacted at  $25^\circ\text{C}$  for 12 hours. The reaction mixture was transferred to water (500 ml), and extraction was carried out with ethyl acetate (150ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/2). Thereby, the title compound (2.47 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.64 (s, 3H), 3.02 (s, 3H), 7.22-7.26 (m, 1H), 7.49-7.66 (m, 5H), 7.91-7.95 (m, 1H)

MS (EI): 299 ( $M +$ , 49 %).

HRMS (EI): calcd for  $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{O}$  299.0825, Found 299.0801.

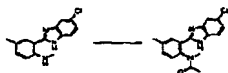
Anal, Calcd for  $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{O}$ : C, 64.11; H, 4.71; N, 14.02.

Found: C, 64.06; H, 4.82; N, 13.80.

(0071)

**Example 16**

N-[2-(6-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide.



Acetyl chloride (282  $\mu\text{l}$ ) was added dropwise to pyridine (20 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (7.1 g) cooled to  $5^\circ\text{C}$  and was reacted at  $25^\circ\text{C}$  for ten



hours. The reaction mixture was transferred to water (100 ml), and it was adjusted to pH 5.0 using 2 N HCl aqueous solution, and extraction was carried out with ethyl acetate (30 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (530 mg) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.63 (s, 3H), 2.43 (s, 3H), 3.00 (s, 3H), 7.23 (dd,  $J$  = 1.9, 8.6 Hz, 1H), 7.35-7.44 (m, 2H), 7.57-7.64 (m, 2H), 7.76 (br, 1H), 12.82 (s, 1H)

MS (EI): 313 ( $M^+$ , 53 %).

HRMS (EI): calcd for  $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}$  313.0982, Found 313.0954.

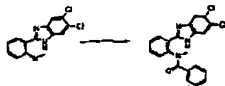
Anal, Calcd for  $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}$ : C, 65.07; H, 5.14; N, 13.39.

Found: C, 64.95; H, 4.97; N, 13.28.

(0072)

#### Example 17

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylbenzamide.



Anhydrous trifluoroacetic acid (1.41 g) was added to dichloromethane (20 ml) solution of 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (1.5 g) and triethylamine (1.85 ml) at 10°C, and it was reacted for 18 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with chloroform (80 ml x 3). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (1.05 g) was obtained as a white solid.

mp: 269-270°C

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.31 (s, 3H), 6.94-6.97 (m, 1H), 7.01-7.06 (m, 2H), 7.17 (m, 1H), 7.37-7.61 (m, 5H), 7.74-7.76 (m, 1H), 7.97 (m, 1H), 12.79 (s, 1H)

MS (EI): 395 ( $M^+$ , 1 %).

HRMS (EI): calcd for  $\text{C}_{21}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}$  395.0592, Found 395.0555.

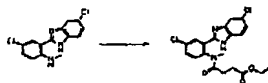
Anal, Calcd for  $\text{C}_{21}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}$ : C, 63.65; H, 3.82; N, 10.60.

Found: C, 63.51; H, 4.06; N, 10.46.

(0073)

#### Example 18

Ethyl 4-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-4-oxo butanoate.



At 25°C, ethyl succinyl chloride (1.06 ml) was added dropwise to pyridine (40 ml) solution of 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (1.99 g) and was reacted for five hours. The reaction mixture was transferred to water (400 ml), and it was adjusted to pH5.0 with hydrochloric acid, and extraction was carried out with ethyl acetate (200 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (673 mg) was obtained as a white solid.

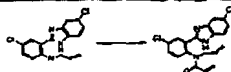
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.06-1.15 (m, 3H), 2.20-2.46 (m, 2H), 2.77-2.79 (m, 2H), 05 (s, 3H), 3.92-4.02 (m, 2H), 7.30-8.07(m, 6H).

MS (FAB+): 420 (M<sup>+</sup>+1, 14 %).

(0074)

#### Example 19

N-allyl-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl] acryl amide.



Acryloyl chloride (638 μl) was added dropwise to dichloromethane (60 ml) solution of N-allyl-4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) aniline (2.5 g) and triethylamine (3.28 ml) cooled to 10°C and was reacted for 16 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml), and the organic layer was separated. The aqueous layer was extracted with chloroform (100 ml), and thereafter was dried with magnesium sulphate, and the recovered organic layer was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1) . Thereby, the title compound (380 mg) was obtained as yellow solid.

mp: 176°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.67 (dd, J = 7.4, 15.0 Hz, 1H), 4.69 (dd, J = 5.4, 15.0 Hz, 1H), 9.4-5.01 (m, 2H), 5.44 (dd, J = 3.2, 9.4 Hz, 1H), 5.71-5.90 (m, 1H), 5.91-6.06 (m, 2H), 7.24 (dd, J = 1.6, 8.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.63-7.67 (m, 2H), 8.08 (d, J = 2.6 Hz, 1H), 12.96 (br, 1H)

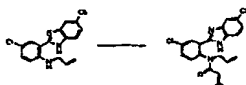
MS (EI): 371 (M<sup>+</sup>, 24 %).

HRMS (EI): calcd for C<sub>19</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O 371.0592, Found 371.0583.

(0075)

#### Example 20

N-allyl-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-3-methyl-2-butene amide.



At 25°C, 3,3-dimethyl acryloyl chloride (669  $\mu$ l) was added dropwise to pyridine (20 ml) solution of N-allyl-4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) aniline (1.47 g) and was reacted for ten hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH7.0 with 1N hydrochloric acid aqueous solution, and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (429 mg) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.50 (s, 3H), 1.59 (s, 3H), 3.69 (dd,  $J$  = 7.5, 15.3 Hz, 1H), 4.68 (dd,  $J$  = 5.5, 15.3 Hz, 1H), 4.98 (d,  $J$  = 3.3 Hz, 1H), 5.03 (s, 1H), 5.27 (s, 1H), 5.78-5.97 (m, 1H), 7.23 (dd,  $J$  = 2.0, 8.6 Hz, 1H), 7.33 (d,  $J$  = 8.3 Hz, 1H), 7.62 (d,  $J$  = 8.6 Hz, 1H), 7.56-7.65 (m, 2H), 7.99 (d,  $J$  = 2.3 Hz, 1H), 12.88 (s, 1H).

(0076)

**Example 21**

N-[4-chloro-2-(6-methyl-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



Acetyl chloride (763  $\mu$ l) was added dropwise to pyridine (40 ml) solution of 4-chloro-N-methyl-2-(5-methyl-1H-benzimidazol-2-yl) aniline (2.43 g) cooled to 5°C and was reacted for two hours. The reaction mixture was transferred to water (200 ml) and was washed with 1N hydrochloric acid aqueous solution and extraction was carried out with chloroform (80 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (2.30 g) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.64 (s, 3H), 2.42 (s, 3H), 3.00 (s, 3H), 7.04-7.07 (m, 1H), 7.38 (m, 1H), 7.46-7.55 (m, 2H), 7.63-7.67 (m, 1H), 8.02 (d,  $J$  = 2.3 Hz, 1H), 12.62 (br, 1H)

MS (EI): 313 ( $M^+$ , 58 %).

HRMS (EI): calcd for  $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}$  313.0982, Found 313.0997.

Anal, Calcd for  $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}$ : C, 65.07; H, 5.14; N, 13.39.

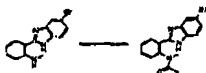
Found: C, 64.82; H, 5.23; N, 13.13.

(0077)

**Example 22**

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N-[2-(6-bromo-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.

At 25°C, acetyl chloride (2.2 ml) was added dropwise to pyridine (40 ml) solution of 2-(5-bromo-1H-benzimidazol-2-yl)-N-methylaniline (4.24 g) and was reacted for eight hours. The reaction mixture was transferred to 1N-HCl aqueous solution (300 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in isopropanol (60 ml) and potassium carbonate (930 mg) was added and was reacted at 25°C for two hours. The reaction mixture was transferred to water (300 ml), and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/2). Thereby, the title compound (1.65 g) was obtained as a white solid.

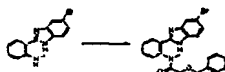
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.64 (s, 3H), 3.02 (s, 3H), 7.34-7.37 (m, 1H), 7.47-7.67 (m, 4H), 7.70-7.86 (m, 1H), 7.87-7.95 (m, 1H), 12.89 (s, 1H)

MS (EI): 343 (M<sup>+</sup>, 65 %).

Anal, Calcd for C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O: C, 55.83; H, 4.10; N, 12.21.

Found: C, 55.80; H, 4.27; N, 12.12.

(0078)

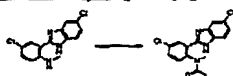
**Example 23**2-(benzyloxy)-N-[2-(6-bromo-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.

At 25°C, benzyloxy acetyl chloride (4.84 ml) was added dropwise to pyridine (50 ml) solution of 2-(5-bromo-1H-benzimidazol-2-yl)-N-methylaniline (3.09 g) and was reacted for 18 hours. The reaction mixture was transferred to 1 N HCl aqueous solution (300 ml), and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (1.16 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.04 (s, 3H), 3.73 (d, J = 14.8 Hz, 1H), 3.85 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 7.10-7.38 (m, 8H), 7.51-7.62 (m, 3H), 7.92-7.95 (m, 1H), 12.93 (br, 1H).

(0079)

## Example 24

N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.

Acetyl chloride 81 ml was added dropwise to pyridine (50 ml) solution of 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (12.05 g) and dimethylaminopyridine (10.1 g) cooled to 10°C and was reacted for eight hours. The reaction mixture was transferred to water (300 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (4.38 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.64 (s, 3H), 3.00 (s, 3H), 7.24-7.27 (m, 1H), 7.55-7.71 (m, 4H), 7.98-8.05 (m, 1H)

MS (FAB): 334 (M<sup>+</sup>+1, 100 %).

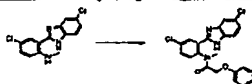
HRMS (FAB) calcd for C<sub>16</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>3</sub>O 334.0514, Found 334.0539.

Anal, Calcd for C<sub>16</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O: C, 57.50; H, 3.92; N, 12.57.

Found: C, 57.52; H, 4.10; N, 12.44.

(0080)

## Example 25

N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-phenoxyacetamido.

At 25°C, phenoxyacetyl chloride (2.08 ml) was added dropwise to pyridine (40 ml) solution of 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (3.38 g) and was reacted for three hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH5.0 with hydrochloric acid, and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (3.21 g) was obtained as yellow solid.

mp: 173°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.04 (s, 3H), 4.30 (d, J = 15.5 Hz, 1H), 4.50 (d, J = 15.5 Hz, 1H), 6.71-6.90 (m, 2H), 7.00-7.06 (m, 1H), 7.31-7.34 (m, 1H), 7.56-7.76 (m, 6H), 8.12 (m, 1H)

MS (FAB): 426 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>22</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 426.0776, Found 426.0789.

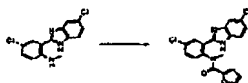
Anal, Calcd for C<sub>22</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: C, 61.71; H, 4.05; N, 9.81.

Found: C, 61.33; H, 4.21; N, 9.56.

(0081)

**Example 26**

N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-furamide.



At 25°C, 2-furoyl chloride (1.22 ml) was added dropwise to pyridine (40 ml) solution of 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (3.30 g) and was reacted for 18 hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH 5.0 with hydrochloric acid and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (2.24 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.22 (s, 3H), 6.08 (bs, 1H), 6.34 (bs, 1H), 7.21-7.24 (m, 1H), 7.45-7.65 (m, 5H), 8.08 (d, J = 1.9 Hz, 1H), 12.82 (s, 1H)

MS (EI): 385 (M<sup>+</sup>, 76 %).

HRMS (EI): calcd for C<sub>19</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 385.0384, Found 385.0414.

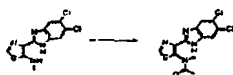
Anal, Calcd for C<sub>19</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: C, 59.09; H, 3.39; N, 10.88.

Found: C, 59.00; H, 3.48; N, 10.79.

(0082)

**Example 27**

N-[4-(5,6-dichloro-1H-benzimidazol-2-yl)-1,3-thiazol-5-yl]-N-methylacetamide.



At 25°C, acetyl chloride (40 μl) was added dropwise to pyridine (5 ml) solution of 4-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methyl-1,3-thiazole-5-amine (170 mg) and was reacted for 14 hours. The reaction mixture was transferred to 1N HCl aqueous solution (80 ml) and extraction was carried out with chloroform (30 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (chloroform / methanol = 30/1). Thereby, the title compound (93 mg) was obtained as slightly yellow solid.

mp: 229°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.83 (s, 3H), 3.19 (s, 3H), 7.69 (s, 1H), 7.93 (s, 1H), 9.30 (s, 1H), 13.27 (s, 1H)

MS (EI): 340 (M<sup>+</sup>, 14 %).

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(0083)

In the same way, the following compounds were obtained.

### Examples 28-52

**Table 1**

IDENT	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	5 <sup>th</sup>	6 <sup>th</sup>	7 <sup>th</sup>	8 <sup>th</sup>	9 <sup>th</sup>	10 <sup>th</sup>	11 <sup>th</sup>	12 <sup>th</sup>	13 <sup>th</sup>	14 <sup>th</sup>	15 <sup>th</sup>	16 <sup>th</sup>	17 <sup>th</sup>	18 <sup>th</sup>	19 <sup>th</sup>	20 <sup>th</sup>	21 <sup>st</sup>	22 <sup>nd</sup>	23 <sup>rd</sup>	24 <sup>th</sup>	25 <sup>th</sup>	26 <sup>th</sup>	27 <sup>th</sup>	28 <sup>th</sup>	29 <sup>th</sup>	30 <sup>th</sup>	31 <sup>st</sup>	32 <sup>nd</sup>	33 <sup>rd</sup>	34 <sup>th</sup>	35 <sup>th</sup>	36 <sup>th</sup>	37 <sup>th</sup>	38 <sup>th</sup>	39 <sup>th</sup>	40 <sup>th</sup>	41 <sup>st</sup>	42 <sup>nd</sup>	43 <sup>rd</sup>	44 <sup>th</sup>	45 <sup>th</sup>	46 <sup>th</sup>	47 <sup>th</sup>	48 <sup>th</sup>	49 <sup>th</sup>	50 <sup>th</sup>	51 <sup>st</sup>	52 <sup>nd</sup>	53 <sup>rd</sup>	54 <sup>th</sup>	55 <sup>th</sup>	56 <sup>th</sup>	57 <sup>th</sup>	58 <sup>th</sup>	59 <sup>th</sup>	60 <sup>th</sup>	61 <sup>st</sup>	62 <sup>nd</sup>	63 <sup>rd</sup>	64 <sup>th</sup>	65 <sup>th</sup>	66 <sup>th</sup>	67 <sup>th</sup>	68 <sup>th</sup>	69 <sup>th</sup>	70 <sup>th</sup>	71 <sup>st</sup>	72 <sup>nd</sup>	73 <sup>rd</sup>	74 <sup>th</sup>	75 <sup>th</sup>	76 <sup>th</sup>	77 <sup>th</sup>	78 <sup>th</sup>	79 <sup>th</sup>	80 <sup>th</sup>	81 <sup>st</sup>	82 <sup>nd</sup>	83 <sup>rd</sup>	84 <sup>th</sup>	85 <sup>th</sup>	86 <sup>th</sup>	87 <sup>th</sup>	88 <sup>th</sup>	89 <sup>th</sup>	90 <sup>th</sup>	91 <sup>st</sup>	92 <sup>nd</sup>	93 <sup>rd</sup>	94 <sup>th</sup>	95 <sup>th</sup>	96 <sup>th</sup>	97 <sup>th</sup>	98 <sup>th</sup>	99 <sup>th</sup>	100 <sup>th</sup>
1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

(0084)

**Table 2**[illegible]

**(0085)**

**Table 3**[illegible]

**1992**

(0086)


**Table 4**[illegible]

100921



(0087)

Table 5

47	H	5'-Cl 6'-Cl	Me	D	<p>Mp: 217-218°C.</p> <p><sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.85(s, 3H, 2H), 1.73(s, 3H), 2.59-0.65(m, 1H), 3.79-3.98(m, 1H), 7.42-7.50(m, 1H), 7.57-7.70(m, 2H), 7.80-7.88(m, 3H).</p> <p>IR (KBr): 3195, 2976, 1641, 1574, 1511, 1490, 1449, 1418, 1385, 1306, 1246, 1091, 966, 867, 847, 777, 682 cm<sup>-1</sup>.</p> <p>MS (EI): 347.04<sup>+</sup>, 38%</p> <p>HRMS (EI): calcd for C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O 347.0692, found 347.0625.</p> <p>Anal. Calcd for C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O: C, 59.64; H, 4.34; N, 12.07.</p> <p>Found: C, 59.58; H, 4.50; N, 11.95.</p>
48	H	5'-Cl 6'-Cl		Me	<p>Mp: 240-253°C.</p> <p><sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.97(s, 3H), 3.04(s, 3H), 4.16(d, J=6Hz, 1H), 4.41(d, J=14.6Hz, 1H), 7.50-7.78(m, 3H), 7.81-8.07(m, 3H).</p> <p>IR (KBr): 3132, 1756, 1657, 1488, 1448, 1426, 1379, 1322, 1096, 1069, 1044, 947, 955, 869, 844, 780, 697 cm<sup>-1</sup>.</p> <p>MS (EI): 391.04<sup>+</sup>, 4%</p> <p>Anal. Calcd for C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>·0.5H<sub>2</sub>O: C, 53.87; H, 4.02; N, 10.47.</p> <p>Found: C, 53.50; H, 4.03; N, 10.31.</p>
49	4'-Cl	5'-Cl	Me	D	<p>Mp: 209-208°C.</p> <p><sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.85(s, 3H, 2H), 1.74(s, 3H), 2.45-0.62(m, 1H), 3.90-3.96(m, 1H), 7.29-7.31(m, 1H), 7.49-7.59(m, 1H), 7.58-7.78(m, 3H), 8.03-8.10(m, 1H).</p> <p>IR (KBr): 3326, 1637, 1458, 1459, 1401, 1309, 1100, 1065, 927, 816, 768 cm<sup>-1</sup>.</p> <p>MS (EI): 347.04<sup>+</sup>, 40%</p> <p>HRMS (EI): calcd for C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O 347.0692, found 347.0604.</p> <p>Anal. Calcd for C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O·0.1H<sub>2</sub>O: C, 59.32; H, 4.35; N, 12.00.</p> <p>Found: C, 59.09; H, 4.50; N, 11.74.</p>

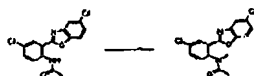
(0088)

Table 6

50	11	8'-Cl 6'-Cl		Me	Mp: 133-135°C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 3.46(s,3H), 1.51(s,3H), 3.16(s,3H), 2.2(s,1H), 7.40-7.44(m,1H), 7.52-7.54(m,2H), 7.82(s,2H), 7.89(ddd, J=1.5, 7.5Hz, 1H), 12.88(br, 1H). MS(EI): 373 (M <sup>+</sup> , 17%). HRMS(EI) calcd for C <sub>19</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>2</sub> O 373.0749, found 373.0781. Anal. Calcd for C <sub>19</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>2</sub> O: C, 60.97; H, 4.68; N, 11.33. Found: C, 60.78; H, 4.78; N, 11.08.
51	4-Cl	8'-Cl		Br	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 0.890(t, 3H), 2.85-3.10(m, 1H), 3.60-4.03(m, 3H), 7.28-7.40(m, 1H), 7.43-7.60(m, 1H), 7.61-7.82(m, 3H), 8.02-8.15(m, 1H). MS (FAB): 364 (M <sup>+</sup> +1, 49%). HRMS (FAB): calcd for C <sub>17</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> 364.0620, found 364.0617.
52	4-CN	8'-Cl	Me	Me	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 1.63(s,3H), 3.00(s,3H), 7.22-7.34(m, 1H), 7.58-7.72(m, 5H), 7.75-7.81(m, 1H), 8.10-8.48(m, 1H), 13.04(br, 1H). MS (FAB): 325 (M <sup>+</sup> +1, 84%).

(0089)

## Example 53

N-[4-chloro-2-(5-chloro-1,3-benzoxazol-2-yl) phenyl]-N-methylacetamide.

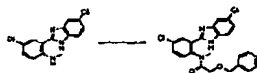
Sodium hydride (317 mg) was added to dimethylformamide (35 ml) solution of N-[4-chloro-2-(5-chloro-1,3-benzoxazol-2-yl) phenyl] acetamide (1.70 g) at 25°C, and it was reacted for 30 minutes. Methyl iodide (526 μl) was added, and stirring was carried out for three hours. The reaction mixture was transferred to water (200 ml). The formed solid was filtered and washed with water and hexane, and it was dried under reduced pressure. Thereby, the title compound (1.61 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.66 (s, 3H), 3.09 (s, 3H), 7.47-7.55 (m, 2H), 7.64-7.67 (m, 1H), 7.81-7.85 (m, 1H), 7.95-7.97 (m, 1H), 8.25-8.26 (m, 1H)

MS (EI): 334 (M<sup>+</sup>, 87 %).

(0090)

## Example 54

2-(benzyloxy)-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.

Benzyloxy acetyl chloride (4.6 ml) was added dropwise to pyridine (60 ml) solution of 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (7.1 g) cooled to 10°C and was reacted for two hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH 5.0 using 2 N HCl aqueous solution, and extraction was carried out with ethyl acetate (150 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (7.03 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.03 (s, 3H), 3.73 (d, J = 14.7 Hz, 1H), 3.86 (d, J = 14.7 Hz, 1H), 4.26 (d, J = 11.9 Hz, 1H), 4.38 (d, J = 11.9 Hz, 1H), 7.09-7.31 (m, 5H), 7.59-7.68 (m, 5H), 8.05-8.06 (m, 1H)

MS (FAB): 440 (M<sup>+</sup>+1, 78 %).

HRMS (FAB): calcd for C<sub>23</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 440.0933, Found 440.0928.

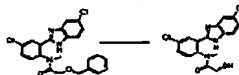
Anal, Calcd for C<sub>23</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: C, 62.74; H, 4.35; N, 9.54.

Found: C, 62.68; H, 4.35; N, 9.42.

(0091)

#### Example 55

N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-2-hydroxy-N-methylacetamide.



Boron tribromide (22.7 ml, 1.0 M dichloromethane solution) was added dropwise to dichloromethane (150 ml) solution of 2-(benzyloxy)-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (5.0 g) cooled to -78°C and was reacted for one hour. The reaction mixture was transferred to water (600 ml), and neutralisation was carried out with 6N sodium hydroxide aqueous solution and extraction was carried out with chloroform (300 ml x 2). The organic layer was washed with water (600 ml x 2) and was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved with chloroform, and hexane was added. A formed solid was washed with hexane, and it was dried under reduced pressure. Recrystallisation was carried out with toluene furthermore and the title compound (931 mg) was obtained as a white solid.

mp: 123-127°C

<sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 3.24 (s, 3H), 3.81 (d, J = 15.7 Hz, 1H), 3.98 (d, J = 15.7 Hz, 1H), 4.45 (s, 1H), 7.12-7.17 (m, 1H), 7.27-7.30 (m, 1H), 7.34-7.37 (m, 1H), 7.51-7.54 (m, 1H), 7.68 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H).

IR (KBr): 3245, 2818, 1639, 1495, 1338, 1227, 1108, 929 cm<sup>-1</sup>.

MS (FAB): 350 (M<sup>+</sup>+1, 59 %).

HRMS(FAB): calcd for  $C_{16}H_{14}Cl_2N_3O_2$  350.0463, Found 350.0492.

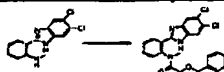
Anal, Calcd for  $C_{16}H_{13}Cl_2N_3O_2/0.15H_2O$ : C, 54.87; H, 3.83; N, 12.00.

Found: C, 54.88; H, 3.74; N, 12.00.

(0092)

**Example 56**

2-(benzyloxy)-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



Benzyloxy acetyl chloride (480  $\mu$ l) was added to pyridine (20 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (740 mg) at 25°C, and it was reacted for one hour. The reaction mixture was transferred to 2N HCl aqueous solution (250 ml), and extraction was carried out with ethyl acetate (100 ml  $\times$  2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was recrystallised using chloroform-hexane. Thereby, the title compound (969 mg) was obtained as a white solid.

$^1H$  NMR (DMSO- $d_6$ ):  $\delta$  3.04 (s, 3H), 3.72 (d,  $J$  = 14.6 Hz, 1H), 3.84 (d,  $J$  = 14.6 Hz, 1H), 4.28 (d,  $J$  = 12.0 Hz, 1H), 4.37 (d,  $J$  = 12.0 Hz, 1H), 7.10-7.16 (m, 2H), 7.19-7.23 (m, 3H), 7.52-7.55 (m, 1H), 7.59-7.64 (m, 2H), 7.76-7.92 (m, 2H), 7.93-7.96 (m, 1H), 13.12 (br, 1H).

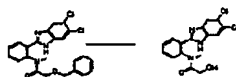
Anal, Calcd for  $C_{23}H_{19}Cl_2N_3O_2$ : C, 62.74; H, 4.35; N, 9.54.

Found: C, 62.77; H, 4.37; N, 9.44.

(0093)

**Example 57**

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-2-hydroxy-N-methylacetamide.



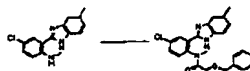
At -78°C, boron tribromide (3.47 ml, 1.0M dichloromethane solution) was added dropwise to dichloromethane (15 ml) solution of 2-(benzyloxy)-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (306 mg). The reaction mixture was transferred to water (100 ml) after having been reacted at -78°C for one hour and extraction was carried out with chloroform (50 ml  $\times$  2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Thereby, the title compound (112 mg) was obtained as a white solid.

$^1H$  NMR (DMSO- $d_6$ ):  $\delta$  3.08 (s, 3H), 3.49 (d,  $J$  = 15.5 Hz, 1H), 3.68 (d,  $J$  = 15.5 Hz, 1H), 7.52-7.55 (m, 1H), 7.61-7.66 (m, 2H), 7.85 (bs, 2H), 7.92-7.95 (m, 1H), 13.13 (br, 1H)

MS (EI): 349 (M +, 1 %).

(0094)

## Example 58

2-(benzyloxy)-N-[4-chloro-2-(6-methyl-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.

Benzyloxy acetyl chloride (5.3 ml) was added dropwise to pyridine (60 ml) solution of 4-chloro-N-methyl-2-(5-methyl-1H-benzimidazol-2-yl) aniline (8.30 g) cooled to 5°C and was reacted for 14 hours. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH7.0 with 1N HCl aqueous solution, and extraction was carried out with chloroform (80 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (5.23 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.42 (s, 3H), 3.03 (s, 3H), 3.73 (d, 1H, J = 14.8 Hz, 1H), 3.87 (d, J = 14.8 Hz, 1H), 4.26 (d, J = 11.9 Hz, 1H), 4.40 (d, J = 11.9 Hz, 1H), 7.04-7.33 (m, 6H), 7.38-7.64 (m, 4H), 8.04 (m, 1H), 12.81 (br, 1H)

MS (FAB): 420 (M<sup>+</sup>+1, 75 %).

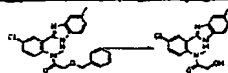
HRMS (FAB): calcd for C<sub>24</sub>H<sub>23</sub>ClN<sub>3</sub>O<sub>2</sub> 420.1479, Found 420.1456.

Anal, Calcd for C<sub>24</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 68.65; H, 5.28; N, 10.01.

Found: C, 68.45; H, 5.25; N, 9.82.

(0095)

## Example 59

N-[4-chloro-2-(5-methyl-1H-benzimidazol-2-yl) phenyl]-2-hydroxy-N-methylacetamide.

Boron tribromide (16.3 ml, 1.0 M dichloromethane solution) was added dropwise to dichloromethane (100 ml) solution of 2-(benzyloxy)-N-[4-chloro-2-(6-methyl-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (4.56 g) cooled to -78°C and was reacted for two hours. The reaction mixture was transferred to water (300 ml), and neutralisation was carried out at potassium hydroxide and extraction was carried out with chloroform (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved with chloroform, and hexane was added. A produced solid was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (821 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.42 (s, 3H), 3.06 (s, 3H), 3.51 (d, 1H, J = 15.1 Hz, 1H), 3.70 (d, J = 15.1 Hz, 1H), 7.04-7.07 (m, 1H), 7.37 (m, 1H), 7.45-7.48 (m, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.65 (dd,

$J = 2.5, 8.5 \text{ Hz, 1H}$ , 8.03 (d,  $J = 2.5 \text{ Hz, 1H}$ )

MS (FAB): 330 ( $M^+ + 1$ , 32 %).

HRMS (FAB): calcd for  $C_{17}H_{17}ClN_3O_2$  330.1009, Found 330.1042.

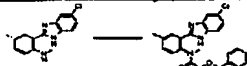
Anal, Calcd for  $C_{17}H_{16}ClN_3O_2 \cdot 0.3H_2O$ : C, 60.91; H, 4.91; N, 12.53.

Found: C, 61.16; H, 5.09; N, 12.53.

(0096)

Example 60

2-(benzyloxy)-N-[2-(6-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide.



Benzyloxy acetyl chloride (3.34 ml) was added dropwise to pyridine (80 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (5.24 g) cooled to  $5^\circ\text{C}$  and was reacted for two hours. The reaction mixture was transferred to 1 N HCl aqueous solution (300 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was washed with 1 N HCl aqueous solution (200 ml x 3) and was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ethyl acetate, and it was dried under reduced pressure. Thereby, the title compound (3.79 g) was obtained as a white solid.

mp:  $161-163^\circ\text{C}$

$^1\text{H NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  2.42 (s, 3H), 3.02 (s, 3H), 3.73 (d,  $J = 14.7 \text{ Hz, 1H}$ ), 3.85 (d,  $J = 14.7 \text{ Hz, 1H}$ ), 4.27 (d,  $J = 12.1 \text{ Hz, 1H}$ ), 4.38 (d,  $J = 12.1 \text{ Hz, 1H}$ ), 7.10-7.14 (m, 1H), 7.19-7.23 (m, 5H), 7.18-7.31 (m, 1H), 7.39 (br, 1H), 7.55-7.66 (m, 2H), 7.77 (br, 1H), 12.87 (br, 1H)

MS (FAB): 420 ( $M^+ + 1$ , 100 %).

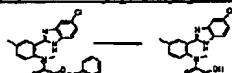
Anal, Calcd for  $C_{24}H_{22}ClN_3O_2 \cdot 0.1H_2O$ : C, 68.35; H, 5.29; N, 9.96.

Found: C, 68.11; H, 5.42; N, 9.72.

(0097)

Example 61

N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-hydroxy-N-methylacetamide.



At  $-78^\circ\text{C}$ , boron tribromide (12.1 ml, 1.0M dichloromethane solution) was added dropwise to dichloromethane (150 ml) solution of 2-(benzyloxy)-N-[2-(6-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide (3.4 g). At  $-78^\circ\text{C}$ , it was reacted for 30 minutes, and thereafter the reaction mixture was transferred to water (500 ml), and it was adjusted to pH 7.0 with potassium hydroxide, and extraction was carried out with chloroform (100 ml x 3). The

organic layer was washed with water and was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Chloroform was added to the residue, and thereafter, hexane was added. The obtained white solid was filtered and was washed with hexane and the title compound (1.93 g) was obtained by causing to dry.

mp: 99°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.43 (s, 3H), 3.06 (s, 3H), 3.50 (d, J = 15.1 Hz, 1H), 3.68 (d, J = 15.1 Hz, 1H), 7.18-7.28 (m, 1H), 7.36-7.46 (m, 2H), 7.56-7.63 (m, 2H), 7.76 (br, 1H)

MS (FAB): 330 (M<sup>+</sup>+1, 46 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>2</sub> 330.1009, Found 330.0992.

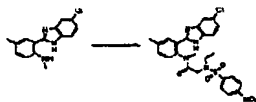
Anal, Calcd for C<sub>17</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub>/0.9H<sub>2</sub>O: C, 59.01; H, 4.93; N, 12.14.

Found: C, 59.29; H, 5.18; N, 11.80.

(0098)

#### Example 62

N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-{ethyl [(4-nitrophenyl) sulphonyl] amino}-N-methylacetamide.



Oxalyl chloride (1.20 ml) was added dropwise to benzene (30 ml) solution of [ethyl (4-nitrophenyl sulphonyl) amino] acetic acid (3.97 g) and pyridine (120 μl) cooled to 10°C, and on completion of the dropwise addition, reaction with heating under reflux was carried out for 30 minutes. The reaction mixture was cooled to room temperature, and thereafter it was concentrated under reduced pressure. The obtained residue was dissolved in dichloromethane (20 ml). The aforesaid dichloromethane solution was added dropwise to pyridine (100 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (3.77 g) cooled to 5°C. On completion of the dropwise addition, reaction temperature was warmed to 25°C, and it was reacted for 16 hours. The reaction mixture was transferred to water (700 ml), and solution was adjusted to pH5.0 with hydrochloric acid, and extraction was carried out with ethyl acetate (300 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (285 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.85 (t, J = 6.9 Hz, 3H), 3.25 (q, J = 6.9 Hz, 2H), 2.46 (s, 3H), 2.91 (s, 3H), 3.81 (d, J = 17.8 Hz, 1H), 3.95 (d, J = 17.8 Hz, 1H), 7.18-7.30 (m, 1H), 7.47-7.58 (m, 4H), 7.74-7.81 (m, 1H), 7.93-8.09 (m, 2H), 8.29-8.32 (m, 2H), 12.09-13.05 (m, 1H).

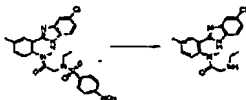
(0099)

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## Example 63

N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-(ethylamino)-N-methylacetamide.



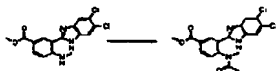
At 25°C, benzene thiol (48 µl) was added to dimethylformamide (5 ml) mixture of N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-[(4-nitrophenyl) sulphonyl] amino}-N-methylacetamide (210 mg) and potassium carbonate (160 mg) and was reacted for three hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (100 ml) and extraction was carried out with ethyl acetate (50 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to chloroform / methanol = 20/1). Thereby, the title compound (73 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.83 (t, J = 6.9 Hz, 3H), 2.34 (q, J = 6.9 Hz, 2H), 2.44 (s, 3H), 91 (d, J = 15.5 Hz, 1H), 3.00 (d, J = 15.5 Hz, 1H), 3.01 (s, 3H), 7.23 (dd, J = 1.9, 8.6 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.42-7.46 (m, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 1.9 Hz, 1H), 7.77 (br, 1H).

(0100)

## Example 64

Methyl 4-[acetyl (methyl) amino]-3-(5,6-dichloro-1H-benzimidazol-2-yl) benzoate.



Acetyl chloride (182 µl) was added to pyridine (5 ml) solution of methyl 3-(5,6-dichloro-1H-benzimidazol-2-yl)-4-(methylanilino) benzoate (600 mg) and dimethylaminopyridine (63 mg) at 25°C, was reacted for 24 hours. The reaction mixture was transferred to 1 N HCl aqueous solution (100 ml) and extraction was carried out with ethyl acetate (30 ml x 3). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (380 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.65 (s, 3H), 3.02 (s, 3H), 3.92 (s, 3H), 7.70 (d, J = 8.1 Hz, 1H), 7.90 (br, 2H), 8.16 (dd, J = 2.1, 8.1 Hz, 1H), 8.55 (d, J = 2.1 Hz, 1H)

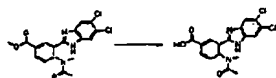
MS (EI): 391 (M<sup>+</sup>, 38 %).

(0101)

## Example 65

4-[acetyl (methyl) amino]-3-(5,6-dichloro-1H-benzimidazol-2-yl) benzoic acid.





A 2 N NaOH aqueous solution (5 ml) was added to methanol (5 ml) solution of methyl 4-[acetyl(methyl)amino]-3-(5,6-dichloro-1H-benzimidazol-2-yl)benzoate (358 mg) and was heated to 80°C and was reacted for four hours. The reaction mixture was cooled to 25°C and transferred to water (80 ml), and extraction was carried out with ethyl acetate (50 ml). The aqueous layer was adjusted to pH 5.0 with 1N-HCl aqueous solution, and extraction was carried out with ethyl acetate (50 ml x 2). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (242 mg) was obtained as a white solid.

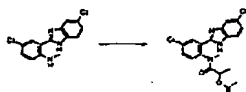
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.65 (s, 3H), 3.02 (s, 3H), 7.66 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 7.93 (s, 1H), 8.13 (dd, J = 1.9, 8.1 Hz, 1H), 8.53 (d, J = 1.9 Hz, 1H)

MS (EI): 377 (M<sup>+</sup>, 60 %).

(0102)

#### Example 66

(1R)-2-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl)-methylanilino]-1-methyl-2-oxoethyl acetate.



At 25°C, (S)-(-)-2-acetoxy propionyl chloride (2.26 g) was added dropwise to pyridine (50 ml) solution of 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (4.0 g) and was reacted for 13 hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH 5.0 with hydrochloric acid, and extraction was carried out with ethyl acetate (150 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (673 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.95 (d, J = 6.2 Hz, 3H), 1.94 (s, 3H), 3.05 (s, 3H), 4.89 (q, J = 6.2 Hz, 1H), 7.23-7.27 (m, 1H), 7.57-7.74 (m, 4H), 8.10-8.12 (m, 1H), 13.05 (br, 1H)

MS (FAB): 406 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>19</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>, 406.0725, Found 406.0722.

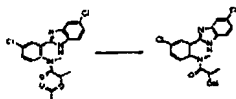
Anal, Calcd for C<sub>19</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>: C, 56.17; H, 4.22; N, 10.34.

Found: C, 55.90; H, 4.28; N, 10.22.

(0103)

## Example 67

(2R)-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-2-hydroxy-N-methylpropane amide.



At 25°C, potassium carbonate (1.96 g) was added to methanol (50 ml) solution of (1R)-2-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-1-methyl-2-oxoethyl acetate (2.88 g), and produced solution was stirred for one hour. The reaction mixture was transferred to water (250 ml) and a produced solid was filtered and was washed with water, and it was dried under reduced pressure. Thereby, the title compound (1.80 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.82 (d, J = 6.2 Hz, 1.5H), 1.05 (d, J = 6.6 Hz, 1.5H), 2.99 (s, 1.5H), 3.04 (s, 1.5H), 3.88-4.03 (m, 1H), 7.19-7.26 (m, 1H), 7.51-7.71 (m, 4H), 7.98-8.06 (m, 1H)

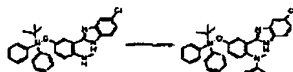
MS (FAB): 364 (M<sup>+</sup>+1, 83 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 364.0619, Found 364.0641.

(0104)

## Example 68

N-[4-[[tert-butyl (diphenyl) silyl] oxy]-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



Acetyl chloride (105 ml) was added to pyridine (10 ml) solution of 4-[[tert-butyl (diphenyl) silyl] oxy]-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (630 mg) at 25°C, and it was reacted for ten minutes. The reaction mixture was transferred to water (200 ml), and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1 to 1/1). Thereby, the title compound (510 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.08 (s, 9H), 1.55 (s, 3H), 2.93 (s, 3H), 6.66 (dd, J = 2.6, 8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.21-7.25 (m, 1H), 7.41-7.52 (m, 6H), 7.56 (d, J = 2.6 Hz, 1H), 7.58-7.65 (m, 1H), 7.67-7.74 (m, 5H), 12.81 (br, 1H)

MS (FAB): 554 (M<sup>+</sup>+1, 2 %).

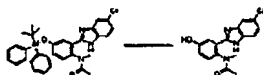
HRMS (FAB): calcd for C<sub>32</sub>H<sub>33</sub>ClN<sub>3</sub>O<sub>2</sub>Si 554.2030, Found 554.2043.

(0105)

## Example 69

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N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-hydroxyphenyl]-N-methylacetamide.

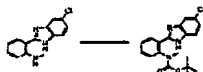
To tetrahydrofuran (60 ml) solution of N-[4-[[tert-butyl (diphenyl) silyl] oxy]-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (500 mg) cooled to 5°C, tetrabutyl ammonium fluoride (1.0 M in THF, 1.17 ml) was added dropwise and was reacted for 30 minutes. The reaction mixture was transferred to saturated aqueous sodium chloride solution (300 ml) and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in chloroform, and hexane was added. A produced solid was washed with hexane, and drying was carried under reduced pressure. Thereby, the title compound (260 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.62 (s, 3H), 2.97 (s, 3H), 6.98 (dd, J = 2.6, 8.6 Hz, 1H), 7.21-7.30 (m, 2H), 7.36-7.39 (m, 1H), 7.52-7.70 (m, 2H), 10.06 (s, 1H), 12.78 (br, 1H)

MS (FAB): 316 (M<sup>+</sup>+1, 4 %).

HRMS (FAB): calcd for C<sub>16</sub>H<sub>15</sub>ClN<sub>3</sub>O<sub>2</sub> 316.0852, Found 316.0866.

(0106)

**Example 70**Tert-butyl 2-(6-chloro-1H-benzimidazol-2-yl) phenyl (methyl) carbamate.

Di-tert-butyl dicarbonate (508 mg) was added to tetrahydrofuran (60 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (500 mg) and dimethylaminopyridine (5 mg) at 25°C, and it was reacted for three hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (150 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (210 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.82 (s, 9H), 3.26 (s, 3H), 7.18-7.84 (m, 7H)

MS (EI): 357 (M<sup>+</sup>, 37 %).

HRMS (EI): calcd for C<sub>19</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>2</sub> 357.1244, Found 357.1244.

Anal, Calcd for C<sub>19</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 63.77; H, 5.63; N, 11.74.

Found: C, 63.64; H, 5.24; N, 12.11.

(0107)

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## Example 71

N-[2-(1H-benzimidazol-2-yl) phenyl]-2,2,2-trifluoro-N-methylacetamide

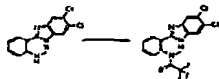
Anhydrous trifluoroacetic acid (1.41 g) was added to dichloromethane (20 ml) solution of N-[2-(1H-benzimidazol-2-yl) phenyl]-N-methylamine (1.5 g) and triethylamine (1.85 ml) at 10°C, and it was reacted for 18 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with chloroform (80 ml x 3). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (1.05 g) was obtained as a white solid.

mp: 175-179°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.25 (s, 3H), 7.15-7.34 (m, 2H), 7.51-7.75 (m, 5H), 8.04-8.13 (m, 1H), 12.89 (br, 1H).

(0108)

## Example 72

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-2,2,2-trifluoro-N-methylacetamide.

Dichloromethane (50 ml) solution of 2-(5,6-dichloro-1H-imidazol-2-yl)-N-methylaniline (1.67 g) and triethylamine (3.98 ml) was cooled to 0°C, and thereafter, trifluoro acetic anhydride (2.42 ml) was added dropwise. It was reacted for three hours at 25°C, and the reaction mixture was transferred to water (300 ml), and extraction was carried out with chloroform (50 ml). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1 to 2/1). Thereby, the title compound (1.23 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.24 (s, 3H), 7.63-7.69 (m, 3H), 7.79-7.88 (m, 2H), 8.05-8.08 (m, 1H), 13.28 (s, 1H)

MS (EI): 387 (M<sup>+</sup>, 13 %).

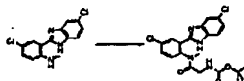
Anal, Calcd for C<sub>16</sub>H<sub>10</sub>Cl<sub>2</sub>F<sub>3</sub>N<sub>3</sub>O: C, 49.51; H, 2.60; N, 10.83.

Found: C, 49.56; H, 2.75; N, 10.71.

(0109)

## Example 73

tert-butyl 2-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-2-oxoethyl carbamate



To tetrahydrofuran (160 ml) solution of Boc-glycine (7.19 g) and 4-methyl morpholine (5.64 ml) cooled to  $-15^{\circ}\text{C}$ , isopropyl chloroformate (6.17 ml) was added dropwise and was reacted for 30 minutes. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (10.0 g) and triethylamine (14.3 ml) were added to the reaction mixture at  $25^{\circ}\text{C}$ , and it was reacted for four days. The reaction mixture was transferred to saturated aqueous sodium chloride solution (800 ml) and extraction was carried out with chloroform (300 ml  $\times$  3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1 to 1/1). Thereby, the title compound (4.83 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.33 (s, 9H), 2.99 (s, 3H), 3.24 (dd,  $J = 4.9, 16.9$  Hz, 1H), 3.53 (dd,  $J = 6.9, 16.9$  Hz, 1H), 6.88 (m, 1H), 7.25-7.28 (m, 1H), 5.57-7.65 (m, 3H), 7.73 (dd,  $J = 2.3, 8.6$  Hz, 1H), 8.05-8.06 (m, 1H), 12.95 (bs, 1H)

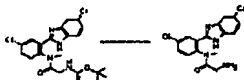
MS (EI): 448 ( $M + 1$  %).

HRMS (EI): calcd for  $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{N}_4\text{O}_3$  449.1147, Found 449.1099.

(0110)

#### Example 74

2-amino-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)phenyl]-N-methylacetamide.



Trifluoroacetic acid (25 ml) was added to tert-butyl 2-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl)methylanilino]-2-oxoethyl carbamate (4.26 g) at  $10^{\circ}\text{C}$ , and a produced solution was stirred for 30 minutes. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH 7.0 by addition of potassium hydroxide, and extraction was carried out with chloroform (100 ml  $\times$  2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (3.11 g) was obtained.

mp:  $101^{\circ}\text{C}$

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.82 (d,  $J = 16.5$  Hz, 1H), 2.98 (d,  $J = 16.5$  Hz, 1H), 3.02 (s, 3H), 7.24 (dd,  $J = 1.9, 8.6$  Hz, 1H), 7.53-7.71 (m, 4H), 8.04 (d,  $J = 2.3$  Hz, 1H)

MS (FAB): 349 ( $M^+ + 1$ , 3 %).

HRMS (FAB): calcd for  $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{N}_4\text{O}_3$  49.0623, Found 349.0626.

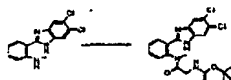
(0111)

#### Example 75

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tert-butyl 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-2-oxoethyl carbamate.



To tetrahydrofuran (10 ml) solution of Boc-glycine (360 mg) and 4-methyl morpholine (282  $\mu$ l) cooled to  $-15^{\circ}\text{C}$  was added dropwise isopropyl chloroformate (251 mg) and was reacted for 15 minutes. 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (500 mg) and triethylamine (477  $\mu$ l) were added to the reaction mixture at  $25^{\circ}\text{C}$ , and it was reacted for 16 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (100 ml) and extraction was carried out with ethyl acetate (50 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (468 mg) was obtained as amorphous solid.

mp:  $123-127^{\circ}\text{C}$

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.33 (s, 9H), 3.01 (s, 3H), 3.23 (dd,  $J = 5.6, 10.1$  Hz, 1H), 3.49 (dd,  $J = 5.6, 10.1$  Hz, 1H), 6.85 (m, 1H), 7.52-7.60 (m, 1H), 7.61-7.72 (m, 2H), 7.84 (s, 1H), 7.97 (dd,  $J = 1.6, 6.9$  Hz, 1H), 13.05 (br, 1H)

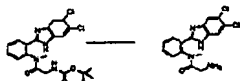
MS (FAB): 449 ( $M^+ + 1$ , 19 %).

HRMS (FAB): calcd for  $\text{C}_{21}\text{H}_{23}\text{Cl}_2\text{N}_4\text{O}_3$  449.1147, Found 449.1171.

(0112)

#### Example 76

2-amino-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide.



At  $10^{\circ}\text{C}$ , trifluoroacetic acid (5 ml) was added to tert-butyl 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-2-oxoethyl carbamate (101 mg), and produced solution was stirred for ten minutes. The reaction mixture was transferred to water (30 ml), and produced white solid was filtered and was washed with water and hexane, and it was dried under reduced pressure. Thereby, the title compound (53 mg) was obtained.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.29 (s, 2H), 2.96 (d,  $J = 15.8$  Hz, 1H), 3.02 (s, 3H), 3.05 (d,  $J = 15.8$  Hz, 1H), 7.14-7.96 (m, 6H)

MS (FAB): 349 ( $M^+ + 1$ , 61 %).

HRMS (FAB): calcd for  $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{N}_4\text{O}$  349.0623, Found 349.0626.

(0113)

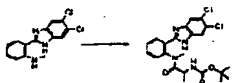
#### Example 77

tert-butyl 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-1-methyl-2-oxoethyl

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carbamate.



To tetrahydrofuran (25 ml) solution of Boc-DL-alanine (1.61 g) and 4-methyl morpholine (1.17 ml) cooled to  $-15^{\circ}\text{C}$ , isopropyl chloroformate (1.13 g) was added dropwise and was reacted for 30 minutes. 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (2.07 g) and triethylamine (2.0 ml) were added to the reaction mixture, and it was reacted at  $25^{\circ}\text{C}$  for 12 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with ethyl acetate (100 ml  $\times$  2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (520 mg) was obtained as a white solid.

mp:  $123-127^{\circ}\text{C}$

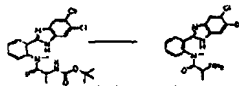
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.74 (d,  $J = 5.4$  Hz, 1.5H), 1.08 (d,  $J = 5.4$  Hz, 1.5H), 1.12 (s, 9H), 3.04 (s, 1.5H), 3.07 (s, 1.5H), 3.86-4.10 (m, 1H), 6.77-6.92 (m, 1H), 7.56-8.13 (m, 5H)

MS (FAB): 463 ( $\text{M}^+ + 1$ , 55 %).

(0114)

#### Example 78

2-amino-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylpropane amide.



Trifluoroacetic acid (5 ml) was added to tert-butyl 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-1-methyl-2-oxoethyl carbamate (380 mg) at  $10^{\circ}\text{C}$ , and produced solution was stirred for 40 minutes. The reaction mixture was transferred to water (100 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide, and extraction was carried out with chloroform (30 ml  $\times$  3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (193 mg) was obtained.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.11 (d,  $J = 6.6$  Hz, 3H), 2.80 (s, 3H), 3.39-3.46 (m, 1H), 7.51-7.96 (m, 6H)

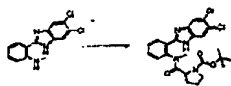
MS (FAB): 363 ( $\text{M}^+ + 1$ , 48 %).

HRMS (FAB): calcd for  $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}$  363.0780, Found 363.0788.

(0115)

## Example 79

tert-butyl 2-([2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino] carbonyl)-1-pyrrolidine carboxylate.



To tetrahydrofuran (25 ml) solution of Boc-DL-proline (1.92 g) and 4-methyl morpholine (1.22 ml) cooled to -15°C was added dropwise isopropyl chloroformate (1.13 g) and was reacted for 30 minutes. 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (2.07 g) and triethylamine (1.18 ml) were added to the reaction mixture, and it was reacted at 25°C for 17 hours. The reaction mixture was transferred to water (250 ml), and extraction was carried out with chloroform (80 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (675 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.46 (s, 9H), 1.70-2.22 (m, 4H), 2.80 (s, 3H), 3.20-3.50 (m, 2H), 4.01-4.07 (m, 1H), 7.50-8.09(m, 6H)

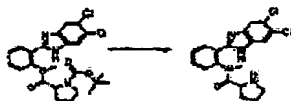
MS (FAB): 489 (M<sup>+</sup>+1, 62 %).

HRMS (FAB): calcd for C<sub>24</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub> 489.1460, Found 489.1487.

(0116)

## Example 80

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-pyrrolidine carboxamido.



Trifluoroacetic acid (3 ml) was added to tert-butyl 2-([2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino] carbonyl)-1-pyrrolidine carboxylate (625 mg) at 10°C, and produced solution was stirred for eight hours. The reaction mixture was transferred to water (100 ml), and it was adjusted to pH 7.0 by addition of potassium hydroxide, and extraction was carried out with chloroform (50 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (469 mg) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.50-1.70 (m, 2H), 1.75-2.05 (m, 2H), 2.95 (s, 3H), 2.75-3.00 (m, 2H), 3.75-3.80 (m, 1H), 7.51-8.03 (m, 6H)

MS (FAB): 389 (M<sup>+</sup>+1, 16 %).

HRMS (FAB): calcd for C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>4</sub>O 389.0935, Found 389.0930.

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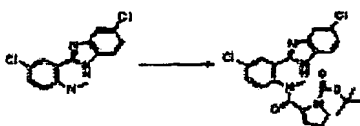
Anal, Calcd for  $C_{19}H_{18}Cl_2N_4O/H_2O$ : C, 56.02; H, 4.95; N, 13.75.

Found: C, 56.00; H, 4.79; N, 13.35.

(0117)

**Example 81**

tert-butyl 2-([4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino] carbonyl)-1-pyrrolidine carboxylate.



To tetrahydrofuran (70 ml) solution of Boc-DL-proline (8.84 g) and 4-methyl morpholine (5.64 ml) cooled to  $-15^{\circ}\text{C}$  was added dropwise isopropyl chloroformate (6.17 ml) and was reacted for 40 minutes. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (10.0 g) and triethylamine (9.53 ml) were added to the reaction mixture, and it was reacted at  $25^{\circ}\text{C}$  for three days. The reaction mixture was transferred to saturated aqueous sodium chloride solution (500 ml) and extraction was carried out with ethyl acetate (150 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1 to 1/1). Thereby, the title compound (6.54 g) was obtained as a white solid.

mp:  $70-73^{\circ}\text{C}$ .

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.30 (s, 9H), 1.72-2.25 (m, 4H), 3.10 (s, 1.5H), 3.14 (s, 1.5H), 3.21-3.43 (m, 2H), 4.02-4.18 (m, 1H), 7.20-8.17 (m, 6H)

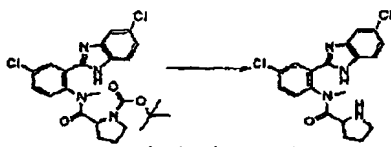
MS (EI): 488 ( $M+3$  %).

HRMS (EI): calcd for  $C_{24}H_{23}Cl_2N_4O_3$ , 488.1382, Found 488.1357.

(0118)

**Example 82**

N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-pyrrolidine carboxamide.



Trifluoroacetic acid (20 ml) was added to tert-butyl 2-([4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino] carbonyl)-1-pyrrolidine carboxylate (6.4 g) at  $10^{\circ}\text{C}$ , and produced solution was stirred for one hour. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH 7.0 by the addition of potassium hydroxide, and extraction was carried out with

chloroform (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (3.88 g) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.58-2.00 (m, 4H), 2.97 (s, 3H), 3.02-3.43 (m, 2H), 4.08-4.18 (m, 1H), 7.28-8.13 (m, 6H)

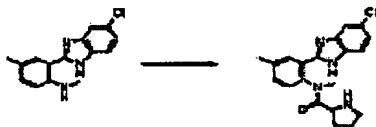
MS (EI): 388 (M<sup>+</sup>, 8 %).

HRMS (EI): calcd for C<sub>19</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O 388.0858, Found 388.0830.

(0119)

#### Example 83

tert-butyl (2S)-2-([2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino] carbonyl)-1-pyrrolidine carboxylate.



To tetrahydrofuran (300 ml) solution of Boc-L-proline (15.0 g) and 4-methyl morpholine (12.1 ml) cooled to -15°C was added dropwise isopropyl chloroformate (9.67 ml) and was reacted for 50 minutes. 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (15.78 g) and triethylamine (24.25 ml) were added to the reaction mixture, and it was reacted at 25°C for 40 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (1.0 l), and extraction was carried out with ethyl acetate (300 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1-2/1). To the thereby obtained product was added trifluoroacetic acid (30 ml), and produced solution was stirred for four hours. The reaction mixture was transferred to water (700 ml), and it was adjusted to pH 7.0 by addition of potassium hydroxide and extraction was carried out with chloroform (50 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was recrystallised using chloroform / hexane. Thereby, the title compound (4.34 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.47-2.03 (m, 4H), 2.39 (s, 1H), 2.43 (s, 2H), 2.67-2.80 (m, 2H), 3.15 (s, 1H), 3.67-3.70 (m, 1H), 3.86 (s, 2H), 7.19-7.83 (m, 6H)

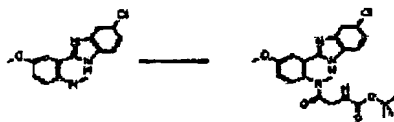
MS (FAB): 369 (M<sup>+</sup>, 43 %).

HRMS (FAB): calcd for C<sub>20</sub>H<sub>22</sub>ClN<sub>4</sub>O 369.1481, Found 369.1480.

(0120)

## Example 84

tert-butyl 2-[2-(6-chloro-1H-benzimidazol-2-yl)-4-methoxymethyl anilino]-2-oxoethyl  
carbamate.



To tetrahydrofuran (60 ml) solution of Boc-glycine (1.43 g) and 4-methyl morpholine (1.22 ml) cooled to  $-15^{\circ}\text{C}$  was added dropwise isopropyl chloroformate (1.34 ml) and was reacted for 30 minutes. 2-(5-chloro-1H-benzimidazol-2-yl)-4-methoxy-N-methylaniline (2.14 g) and triethylamine (3.09 ml) were added to the reaction mixture, and it was reacted at  $25^{\circ}\text{C}$  for 16 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (150 ml) and extraction was carried out with ethyl acetate (50 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (1.41 g) was obtained as a white solid.

mp:  $128^{\circ}\text{C}$

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.34 (s, 9H), 2.98 (s, 3H), 3.23 (dd,  $J = 5.2, 16.4$  Hz, 1H), 3.52 (dd,  $J = 6.1, 16.4$  Hz, 1H), 3.89 (s, 3H), 6.81 (m, 1H), 7.20 (dd,  $J = 2.9, 8.6$  Hz, 1H), 7.23-31 (m, 1H), 7.45 (d,  $J = 8.6$  Hz, 1H), 7.50 (d,  $J = 2.9$  Hz, 1H), 7.56-7.68 (m, 2H), 12.88 (br, 1H)

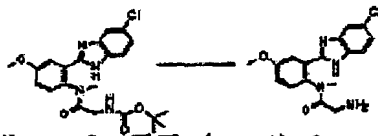
MS (FAB): 445 ( $\text{M}^+ + 1$ , 100 %).

HRMS (FAB): calcd for  $\text{C}_{22}\text{H}_{26}\text{ClN}_4\text{O}_4$  445.1643, Found 445.1661.

(0121)

## Example 85

2-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methoxyphenyl]-N-methylacetamide.



Trifluoroacetic acid (10 ml) was added to tert-butyl 2-[2-(6-chloro-1H-benzimidazol-2-yl)-4-methoxymethyl anilino]-2-oxoethyl carbamate (1.30 g) at  $10^{\circ}\text{C}$ , and produced solution was stirred for 30 minutes. The reaction mixture was transferred to water (100 ml), and it was adjusted to pH7.0 with potassium hydroxide, and extraction was carried out with chloroform (50 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Chloroform was added to produced oil, and furthermore, hexane was added. Produced white solid was filtered and was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (732 mg) was obtained.

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mp: 139°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.82 (d, J = 16.4 Hz, 1H), 2.95 (d, J = 16.4 Hz, 1H), 3.01 (s, 3H), 3.88 (s, 3H), 7.16 (dd, J = 2.9, 8.9 Hz, 1H), 7.23 (dd, J = 1.9, 8.6 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.47 (d, J = 1.9, 8.6 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H)

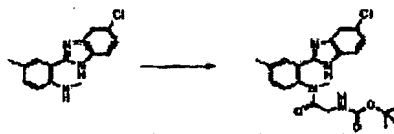
MS (FAB): 345 (M<sup>+</sup>+1, 100 %).

HRMS (FAB)= calcd for C<sub>17</sub>H<sub>18</sub>ClN<sub>4</sub>O<sub>2</sub> 345.1118, Found 345.1128.

(0122)

#### Example 86

tert-butyl 2-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-2-oxoethyl carbamate.



To tetrahydrofuran (160 ml) solution of Boc-glycine (8.43 g) and 4-methyl morpholine (6.61 ml) cooled to -20°C was added dropwise isopropyl chloroformate (7.23 ml) and was reacted for 30 minutes. 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (10.9 g) and triethylamine (16.76 ml) were added to the reaction mixture, and it was reacted at 25°C for 18 hours. The reaction mixture was transferred to water (300 ml), and extraction was carried out with chloroform (150 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 3/1 to 1/1). Thereby, the title compound (6.50 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.34 (s, 9H), 2.44 (s, 3H), 2.98 (s, 3H), 3.24 (dd, J = 7.30, 16.5 Hz, 1H), 3.52 (dd, J = 6.1, 16.5 Hz, 1H), 6.85 (bt, 1H), 7.24 (dd, J = 2.0, 8.6 Hz, 1H), 7.38-7.49 (m, 1H), 7.55-7.62 (m, 2H), 7.79 (br, 1H), 12.80 (br, 1H)

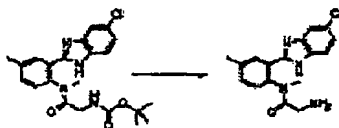
MS (FAB): 429 (M<sup>+</sup>+1, 49 %).

HRMS (FAB): calcd for C<sub>22</sub>H<sub>26</sub>ClN<sub>4</sub>O<sub>3</sub> 429.1693, Found 429.1661.

(0123)

#### Example 87

2-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide.



Trifluoroacetic acid (30 ml) was added to tert-butyl 2-[2-(6-chloro-1H-benzimidazol-2-yl)-4-

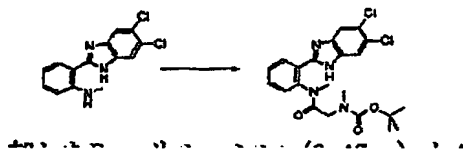
dimethyl anilino]-2-oxoethyl carbamate (6.0 g) at 10°C, and produced solution was stirred for one hour. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide, and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was recrystallised at hexane / chloroform, and it was dried under reduced pressure. Thereby, the title compound (3.82 g) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.46 (s, 3H), 3.04 (s, 3H), 3.29-3.47 (m, 2H), 7.24-7.27 (m, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.48-7.52 (m, 1H), 7.57-7.67 (m, 2H), 7.83 (br, 1H), 00 (br, 1H).

(0124)

**Example 88**

tert-butyl 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-2-oxoethyl (methyl) carbamate.



To tetrahydrofuran (150 ml) solution of Boc-sarcosine (6.47 g) and 4-methyl morpholine (7.52 ml) cooled to -15°C was added dropwise isopropyl chloroformate (4.27 ml) and was reacted for 30 minutes. 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (10.0 g) and triethylamine (9.53 ml) were added to the reaction mixture, and it was reacted at 25°C for 23 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (500 ml) and extraction was carried out with chloroform (100 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1 to 1/1). Thereby, the title compound (3.32 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.19 (s, 4.5H), 1.36 (s, 4.5H), 2.63 (s, 1.5H), 2.73 (s, 1.5H), 95 (s, 1.5H), 3.07 (s, 1.5H), 3.28-3.38 (m, 0.5H), 3.41-3.49 (m, 0.5H), 3.67-3.74 (m, 0.5H), 3.87-3.93 (m, 0.5H), 7.51-7.98 (m, 6H)

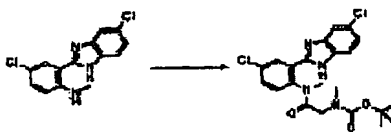
MS (EI): 462 (M +, 1 %), 495 (M +, 73, 4 %).

HRMS (EI): calcd for C<sub>22</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>, 462.1226, Found 462.1180.

(0125)

**Example 89**

tert-butyl 2-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-2-oxoethyl (methyl) carbamate.



To tetrahydrofuran (50 ml) solution of Boc-sarcosine (2.27 g) and 4-methyl morpholine (2.03 ml) cooled to  $-15^{\circ}\text{C}$  was added dropwise isopropyl chloroformate (1.67 ml) and was reacted for one hour. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (2.70 g) and tetrahydrofuran (50 ml) solution of triethylamine (2.58 ml) were added to the reaction mixture, and it was reacted at  $25^{\circ}\text{C}$  for five days. The reaction mixture was transferred to saturated aqueous sodium chloride solution (300 ml) and extraction was carried out with ethyl acetate (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1 to 1/1). Thereby, the title compound (1.80 g) was obtained as a white solid.

mp:  $99^{\circ}\text{C}$

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.18 (s, 4.5H), 1.37 (s, 4.5H), 2.63 (s, 1.5H), 2.72 (s, 1.5H), 9.4 (s, 1.5H), 3.05 (s, 1.5H), 3.43-3.54(m, 1H), 3.70-3.77(m, 0.5H), 3.90-3.98(m, 0.5H), 7.25-7.30 (m, 1H), 7.55-7.67 (m, 3H), 7.72-7.78 (m, 1H), 8.08-8.13(m, 1H)

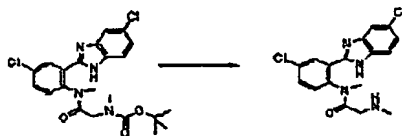
MS (FAB): 463 ( $\text{M}^{++}$ 1, 63 %).

HRMS (FAB): calcd for  $\text{C}_{22}\text{H}_{25}\text{Cl}_2\text{N}_4\text{O}_3$  463.1304, Found 463.1340.

(0126)

#### Example 90

N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-(methylamino) acetamide.



Trifluoroacetic acid (20 ml) was added to tert-butyl 2-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-2-oxoethyl (methyl) carbamate (1.80 g) at  $10^{\circ}\text{C}$ , and produced solution was stirred for one hour. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH7.0 with potassium hydroxide, and extraction was carried out with chloroform (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Chloroform was added to produced oil, and furthermore, hexane was added. Produced white solid was filtered and was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (1.13 g) was obtained.

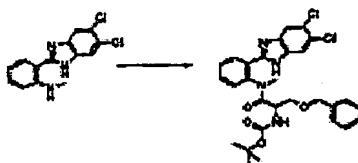
mp:  $99^{\circ}\text{C}$

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.09 (s, 3H), 2.83-3.03 (m, 2H), 3.03 (s, 3H), 7.25 (dd,  $J = 1.9, 8.6$  Hz, 1H), 7.55-7.65 (m, 3H), 7.70 (dd,  $J = 2.5, 8.5$  Hz, 1H), 8.05 (d,  $J = 2.5$  Hz, 1H)  
MS (EI): 362 ( $M + 32$  %).

(0127)

## Example 91

tert-butyl 1-[(benzyloxy) methyl]-2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-2-oxoethyl carbamate.



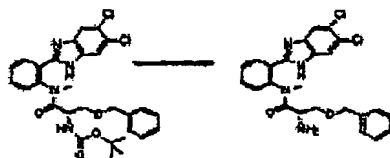
To tetrahydrofuran (180 ml) solution of Boc-O-benzyl-L-serine (10.9 g) and 4-methyl morpholine (5.08 ml) cooled to  $-15^\circ\text{C}$  was added dropwise isopropyl chloroformate (5.55 ml) and was reacted for 30 minutes. 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (9.0 g) and triethylamine (12.8 ml) were added to the reaction mixture, and it was reacted at  $25^\circ\text{C}$  for 50 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (700 ml) and extraction was carried out with chloroform (300 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 20/1 to 2/1). Thereby, the title compound (2.04 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.01 (s, 6H), 1.33 (s, 3H), 3.06 (s, 1.5H), 3.14 (s, 1.5H), 3.26-3.56 (m, 2H), 3.97 (s, 1H), 4.24 (s, 1H), 4.13-4.35 (m, 1H), 6.92-8.08 (m, 11H)  
MS (FAB): 569 ( $M^+ + 1$ , 1 %), 496 ( $M + 73$ , 4 %).

(0128)

## Example 92

2-amino-3-(benzyloxy)-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylpropane amide.



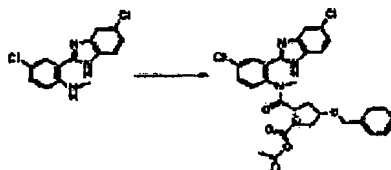
Trifluoroacetic acid (20 ml) was added to tert-butyl 1-[(benzyloxy) methyl]-2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-2-oxoethyl carbamate (2.0 g) at  $10^\circ\text{C}$ , and produced

solution was stirred for eight hours. The reaction mixture was transferred to water (250 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide, and extraction was carried out with chloroform (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was washed with ether, and it was dried under reduced pressure. Thereby, the title compound (1.23 g) was obtained. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.82 (s, 3H), 3.19-3.37 (m, 1H), 3.52-3.57 (m, 1H), 3.63-3.69 (m, 1H), 4.44 (s, 2H), 7.24-7.40 (m, 7H), 7.54-7.70 (m, 2H), 7.88-7.90(m, 2H). MS (FAB): 469 (M<sup>+</sup>+1, 22 %). HRMS (FAB): calcd for C<sub>24</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub> 469.1198, Found 469.1170.

(0129)

## Example 93

tert-butyl (2R,4R)-4-(benzyloxy)-2-([4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)] methyl anilino) carbonyl]-1-pyrrolidine carboxylate.



To tetrahydrofuran (60 ml) solution of N-α-tert butoxycarbonyl-O-benzyl-trans-4-hydroxy-L-proline (24.0 g) and 4-methyl morpholine (13.67 ml) cooled to -15°C was added dropwise isopropyl chloroformate (11.2 ml) and was reacted for one hour. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (18.18 g) and triethylamine (17.3 ml) were added to the reaction mixture, and it was reacted at 25°C for three days. The reaction mixture was transferred to saturated aqueous sodium chloride solution (500 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 20/1 to 1/1). Thereby, the title compound (3.82 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.36 (s, 4.5H), 1.45 (s, 4.5H), 2.16-2.27(m, 2H), 3.12 (s, 1.5H), 3.17 (s, 1.5H), 3.35-3.58(m, 2H), 3.76-3.93(m, 1H), 4.17 (s, 1H), 4.02-4.32 (m, 1H), 4.42 (s, 1H), 7.05-8.18(m, 11H)

MS (FAB): 595 (M<sup>+</sup>+1, 13 %).

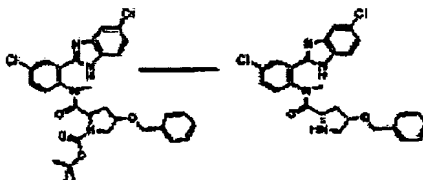
(0130)

## Example 94

(2R, 4S)-4-( benzyloxy)-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)] phenyl]-N-methyl-2-



pyrrolidine carboxamido.



At 10°C, trifluoroacetic acid (10 ml) was added to tert-butyl (2R,4R)-4-(benzyloxy)-2-[[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) methylanilino] carbonyl]-1-pyrrolidine carboxylate (3.70 g) and produced solution was stirred for four hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide, and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in chloroform, and hexane was added. A produced solid was filtered and was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (3.20 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.04-2.12 (m, 2H), 2.98 (s, 3H), 3.24-3.42 (m, 2H), 4.09-4.41 (m, 4H), 7.04-8.18(m, 11H)

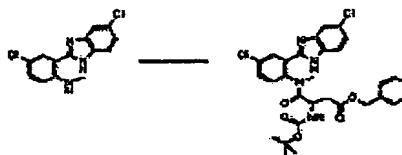
MS (FAB): 495 (M<sup>+</sup>+1, 30 %).

HRMS (FAB): calcd for C<sub>26</sub>H<sub>25</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub> 495.1365, Found 495.1328.

(0131)

#### Example 95

Benzyl (3S)-3-[[tert butoxycarbonyl] amino]-4-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-4-oxo butanoate.



To tetrahydrofuran (70 ml) solution of Boc-D-Asp(OBn)-OH (13.3 g) and 4-methyl morpholine (7.52 ml) cooled to -20°C was added dropwise isopropyl chloroformate (6.16 ml) and was reacted for three hours. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (10.0 g) and triethylamine (9.53 ml) were added to the reaction mixture, and it was reacted at 25°C for five days. The reaction mixture was transferred to saturated aqueous sodium chloride solution (400 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1 to ©Rising Sun Communications Ltd.

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2/1). Thereby, the title compound (1.51 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.95 (s, 4.5H), 1.32 (s, 4.5H), 2.33-2.57(m, 1H), 2.63-2.76(m, 0.5H), 2.80-2.90(m, 0.5H), 2.96 (s, 1.5H), 3.02 (s, 1.5H), 3.40-3.44(m, 1H), 4.73-4.82 (m, 1H), 5.02-5.08 (m, 1H), 7.08-8.15(m, 11H)

MS (FAB): 597 (M<sup>+</sup>+1, 10 %).

HRMS (FAB): calcd for C<sub>30</sub>H<sub>31</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>5</sub>, 597.1672, Found 597.1699.

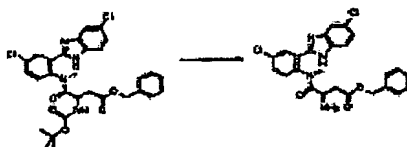
Anal, Calcd for C<sub>30</sub>H<sub>30</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>5</sub>•0.5H<sub>2</sub>O: C, 59.41; H, 5.16; N, 9.23..

Found: C, 59.03; H, 5.05; N, 9.12.

(0132)

**Example 96**

Benzyl (3S)-3-amino-4-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) methylanilino]-4-oxo butanoate.



Trifluoroacetic acid (3 ml) was added to benzyl (3S)-3-[(tert-butoxycarbonyl) amino]-4-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-4-oxo butanoate (250 mg) at 10°C, and produced solution was stirred for three hours. The reaction mixture was transferred to water (100 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide and extraction was carried out with ethyl acetate (50 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (93 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.53 (dd, J = 5.6, 16.5 Hz, 1H), 2.74 (s, 3H), 2.92 (dd, J = 6, 16.5 Hz, 1H), 3.78 (dd, J = 5.6, 8.6 Hz, 1H), 5.08 (d, J = 12.5 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 7.23-7.43 (m, 6H), 7.57-7.71 (m, 4H), 7.94 (d, J = 2.3 Hz, 1H)

MS (FAB): 497 (M<sup>+</sup>+1, 9 %).

HRMS (FAB): calcd for C<sub>25</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>, 497.1147, Found 497.1137.

Anal, Calcd for C<sub>25</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>: C, 60.37; H, 4.46; N, 11.26.

Found: C, 60.20; H, 4.45; N, 11.32.

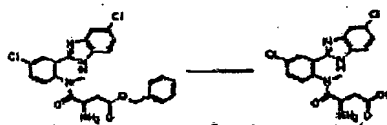
(0133)

**Example 97**

(3S)-3-amino-4-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) methylanilino]-4-oxo butanoic acid.

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A mixture of benzyl (3S)-3-amino-4-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)methylanilino]-4-oxo butanoate (160 mg), 10 % Pd-C (100 mg) and ethanol (15 ml) was reacted under hydrogen atmosphere for two hours. The reaction mixture was filtered using celite, and the filtrate was concentrated, and the obtained residue was washed with chloroform, and it was dried under reduced pressure. Thereby, the title compound (128 mg) was obtained as a white solid.

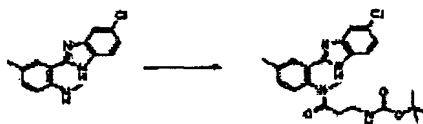
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.34-2.43 (m, 1H), 2.64-2.75 (m, 1H), 2.81 (s, 3H), 2.84 (m, 1H), 7.24-7.29 (m, 1H), 7.57-7.78 (m, 4H), 7.99 (d,  $J = 2.6$  Hz, 1H)

MS (FAB): 407 ( $M^+ + 1$ , 7 %).

(0134)

#### Example 98

tert-butyl 3-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-3-oxopropyl carbamate.



To tetrahydrofuran (70 ml) solution of Boc- $\beta$ -alanine (2.46 g) and 4-methyl morpholine (1.8 ml) cooled to  $-20^\circ\text{C}$  was added dropwise isopropyl chloroformate (2.0 ml) and was reacted for one hour. 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (2.95 g) and triethylamine (4.6 ml) were added to the reaction mixture, and it was reacted at  $25^\circ\text{C}$  for two days. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with ethyl acetate (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (2.98 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.31 (s, 9H), 2.38 (s, 3H), 2.84 (s, 1.5H), 2.86 (s, 1.5H), 3.03-3.28 (m, 4H), 7.37-8.09 (m, 6H)

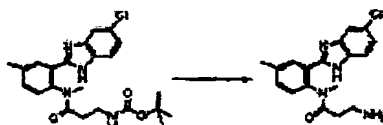
MS (FAB): 443 ( $M^+ + 1$ , 32 %).

HRMS (FAB): calcd for  $\text{C}_{23}\text{H}_{28}\text{ClN}_4\text{O}_3$  443.1849, Found 443.1879.

(0135)

#### Example 99

3-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylpropane amide.



Trifluoroacetic acid (25 ml) was added to tert-butyl 3-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-3-oxopropyl carbamate (2.5 g) at 10°C, and produced solution was stirred for one hour. The reaction mixture was transferred to water (150 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide, and extraction was carried out with ethyl acetate (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was recrystallised at hexane / chloroform, and it was dried under reduced pressure. Thereby, the title compound (1.80 g) was obtained.

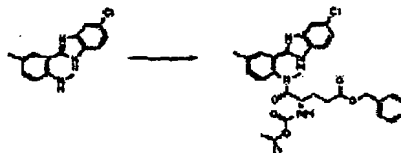
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.32-2.38 (m, 2H), 2.44 (s, 3H), 2.95 (s, 3H), 2.87-3.02 (m, 2H), 7.24-7.27 (m, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 1.7, 8.3 Hz, 1H), 7.55-7.77 (m, 4H), 7.84 (m, 1H), 13.18 (br, 1H).

HRMS (FAB): calcd for C<sub>18</sub>H<sub>20</sub>ClN<sub>4</sub>O<sub>3</sub>, 43.1325, Found 343.1318.

(0136)

#### Example 100

Benzyl (4R)-4-[(tert-butoxycarbonyl) amino]-5-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-5-oxo-pentanoate.



At -20°C, isopropyl chloroformate (4.31 ml) was added dropwise to tetrahydrofuran (100 ml) solution of Boc-L-Glu(OBn)-OH (9.68 g) and 4-methyl morpholine (3.94 ml) and was reacted for one hour. 2-(5-chloro-1H-benzimidazol-2-yl)-N,4-dimethylaniline (6.50 g) and triethylamine (10.0 ml) were added to the reaction mixture at 25°C, and it was reacted for two days. The reaction mixture was transferred to water (300 ml), and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (1.98 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.09 (s, 4.5H), 1.32 (s, 4.5H), 2.09-2.39 (m, 4H), 2.43 (s, 3H), 2.97 (s, 1.5H), 3.02 (s, 1.5H), 3.96-4.12(m, 1H), 4.73-5.12(m, 2H), 7.16-7.86(m, 11H)

MS (FAB): 591 (M<sup>+</sup>+1, 29 %).

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HRMS (FAB): calcd for  $C_{32}H_{36}ClN_4O_5$ , 591.2374, Found 591.2349.

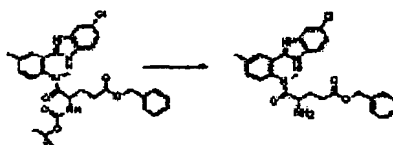
Anal, Calcd for  $C_{32}H_{35}ClN_4O_5$ : C, 65.02; H, 5.97; N, 9.48.

Found: C, 64.77; H, 5.76; N, 9.36.

(0137)

**Example 101**

Benzyl (4R)-4-amino-5-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-5-oxo pentanoate.



Trifluoroacetic acid (30 ml) was added to benzyl (4R)-4-[(tert butoxycarbonyl) amino]-5-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-5-oxo pentanoate (1.70 g) at  $-5^{\circ}\text{C}$ , and produced solution was stirred for five hours. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide and extraction was carried out with ethyl acetate (80 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (1.60 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.68-1.86 (m, 1H), 1.88-2.01 (m, 1H), 2.17-2.27(m, 1H), 2.30-2.43(m, 1H), 2.41 (s, 3H), 2.81 (s, 3H), 4.68-4.88(m, 1H), 5.05 (s, 2H), 7.13-7.71(m, 11H)

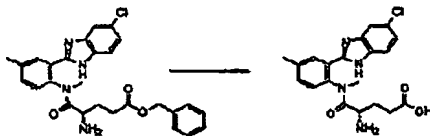
MS (FAB): 491 ( $M^+ + 1$ , 13 %).

HRMS (FAB): calcd for  $C_{27}H_{28}ClN_4O_3$ , 491.1849, Found 491.1847.

(0138)

**Example 102**

(4R)-4-amino-5-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-5-oxo pentanoic acid.



A mixture of benzyl (4R)-4-amino-5-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-5-oxo pentanoate (1.60 g), 10 % Pd-C (200 mg) and methanol (25 ml) was reacted under hydrogen atmosphere for three hours. The reaction mixture was filtered using celite, and the filtrate was concentrated, and the obtained residue was washed with chloroform, and it was dried under reduced pressure. Thereby, the title compound (820 mg) was obtained as a white solid.

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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.48-1.63 (m, 1H), 1.70-1.98 (m, 2H), 2.10-2.18(m, 1H), 2.45 (s, 3H), 2.86 (s, 3H), 3.63-3.69(m, 1H), 7.17-7.30(m, 2H), 7.42-7.48(m, 1H), 7.55-7.66 (m, 2H), 7.73-7.76(m, 1H)

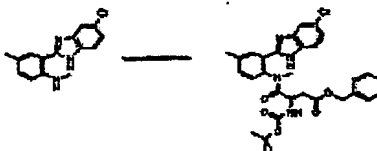
MS (FAB): 401 (M<sup>+</sup>+1, 22 %).

HRMS (FAB): calcd for C<sub>20</sub>H<sub>22</sub>ClN<sub>4</sub>O<sub>3</sub> 401.1380, Found 401.1378.

(0139)

Example 103

Benzyl (3R)-3-[(tert butoxycarbonyl) amino]-4-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-4-oxo butanoate.



At -20°C, isopropyl chloroformate (9.1 ml) was added dropwise to tetrahydrofuran (200 ml) solution of Boc-L-Asp(OBn)-OH (22.1 g) and 4-methyl morpholine (9.4 ml) and was reacted for 40 minutes. 2-(5-chloro-1H-benzimidazol-2-yl)-N, 4-dimethylaniline (15.5 g) and triethylamine (23.8 ml) were added to the reaction mixture, and it was reacted at 25°C for two days. The reaction mixture was transferred to water (600 ml), and extraction was carried out with ethyl acetate (200 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (3.39 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.99 (s, 4.5H), 1.33 (s, 4.5H), 2.40 (s, 1.5H), 2.36-2.40(m, 0.5H), 2.41 (s, 1.5H), 2.47-2.58(m, 0.5H), 2.68-2.77(m, 0.5H), 2.83-2.89 (m, 0.5H), 90 (s, 1.5H), 2.98 (s, 1.5H), 4.39-4.53 (m, 1H), 4.79-5.07 (m, 2H), 7.07-7.88 (m, 11H)

MS (FAB): 577 (M<sup>+</sup>+1, 21 %).

HRMS (FAB): calcd for C<sub>31</sub>H<sub>34</sub>ClN<sub>4</sub>O<sub>5</sub> 577.2217, Found 577.2230.

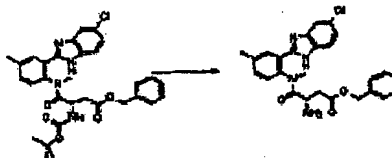
Anal, Calcd for C<sub>31</sub>H<sub>33</sub>ClN<sub>4</sub>O<sub>5</sub>: C, 64.52; H, 5.76; N, 9.71.

Found: C, 64.45; H, 5.75; N, 9.71.

(0140)

Example 104

Benzyl (3R)-3-amino-4-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-4-oxo butanoate.



Trifluoroacetic acid (40 ml) was added to benzyl (3R)-3-[(tert butoxycarbonyl) amino]-4-[2-(6-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-4-oxo butanoate (3.39 g) at 10°C, and produced solution was stirred for three hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH7.0 by addition of potassium hydroxide and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (2.74 g) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.41 (s, 3H), 2.53 (dd, J = 5.6, 16.3 Hz, 1H), 2.72 (s, 3H), 2.92 (dd, J = 8.9, 16.3 Hz, 1H), 3.82 (dd, J = 5.6, 8.9 Hz, 1H), 5.08 (d, J = 12.5 Hz, 1H), 5.15 (d, J = 12.5 Hz, 1H), 7.20-7.27 (m, 2H), 7.34-7.42 (m, 6H), 7.58-7.70(m, 3H)

MS (FAB): 477 (M<sup>+</sup>+1, 28 %).

HRMS (FAB): calcd for C<sub>26</sub>H<sub>26</sub>ClN<sub>4</sub>O<sub>3</sub>, 477.1693, Found 477.1682.

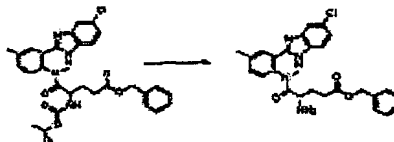
Anal, Calcd for C<sub>26</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>3</sub>: C, 65.47; H, 5.28; N, 11.75.

Found: C, 65.44; H, 5.39; N, 11.80.

(0141)

#### Example 105

(3R)-3-amino-4-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-4-oxo butanoic acid



A mixture of benzyl (3R)-3-amino-4-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-4-oxo butanoate (2.70 g), 10 % Pd-C (280 mg) and methanol (90 ml) was reacted under hydrogen atmosphere for two hours. The reaction mixture was filtered using celite, and the filtrate was concentrated, and the obtained residue was washed with chloroform, and it was dried under reduced pressure. Thereby, the title compound (2.10 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.26-2.38 (m, 1H), 2.43 (s, 3H), 2.55-2.63 (m, 1H), 2.83 (s, 3H), 3.97-4.08 (m, 1H), 7.17-7.30 (m, 1H), 7.43-7.68 (m, 4H), 7.75-7.82(m, 1H)

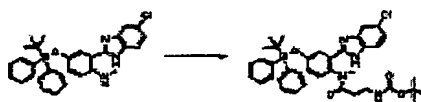
MS (FAB): 387 (M<sup>+</sup>+1, 16 %).

HRMS (FAB): calcd for C<sub>19</sub>H<sub>20</sub>ClN<sub>4</sub>O<sub>3</sub>, 387.1223, Found 387.1226.

(0142)

## Example 106

tert-butyl 3-[4-[tert-butyl (diphenyl) silyl]-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-3-oxopropyl carbamate.



To tetrahydrofuran (20 ml) solution of Boc- $\beta$ -alanine (384 mg) and 4-methyl morpholine (293  $\mu$ l) cooled to  $-20^{\circ}\text{C}$  was added dropwise isopropyl chloroformate (293  $\mu$ l) and was reacted for one hour. Tetrahydrofuran (10 ml) solution of 4-[[tert-butyl (diphenyl) silyl] oxy]-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (900 mg) and triethylamine (732  $\mu$ l) were added to the reaction mixture, and it was reacted at  $25^{\circ}\text{C}$  for 16 hours. The reaction mixture was transferred to water (300 ml), and extraction was carried out with ethyl acetate (150 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved isopropyl alcohol (80 ml), and potassium carbonate (2.0 g) was added. At  $25^{\circ}\text{C}$ , it was stirred for two hours, and thereafter it was transferred to water (150 ml), and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. It was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1 to 1/1). Thereby, the title compound (410 mg) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.09 (s, 9H), 1.27 (s, 9H), 1.96-2.11 (m, 2H), 2.86 (s, 3H), 2.99-3.13 (m, 2H), 6.58-6.63 (m, 1H), 6.64 (dd,  $J = 2.9, 8.6$  Hz, 1H), 7.15 (d,  $J = 8.6$  Hz, 1H), 7.22-7.26 (m, 1H), 7.42-7.53 (m, 6H), 7.59 (d,  $J = 2.9$  Hz, 1H), 7.61 (m, 1H), 7.67-7.77 (m, 5H), 12.90 (br, 1H)

MS (FAB): 683 ( $M^+ + 1$ , 3 %).

HRMS (FAB): calcd for  $\text{C}_{38}\text{H}_{44}\text{ClN}_4\text{O}_4\text{Si}$  683.2820, Found 683.2785.

(0143)

## Example 107

tert-butyl 3-[2-(5-chloro-1H-benzimidazol-2-yl)-4-hydroxymethyl anilino]-3-oxopropyl carbamate.



To tetrahydrofuran (30 ml) solution of tert-butyl 3-[4-[tert-butyl (diphenyl) silyl]-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-3-oxopropyl carbamate (400 mg) cooled to  $5^{\circ}\text{C}$  was added

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dropwise tetrabutyl ammonium fluoride (1.0M in THF, 878  $\mu$ l) and was reacted for ten minutes. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in chloroform, and hexane was added. A produced solid was washed with hexane, and drying was carried under reduced pressure. Thereby, the title compound (250 mg) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.29 (s, 9H), 2.06-2.18 (m, 2H), 2.88 (s, 3H), 3.05-3.22 (m, 2H), 6.96 (dd,  $J$  = 2.6, 8.6 Hz, 1H), 7.17-7.26 (m, 2H), 7.31-7.39 (m, 1H), 7.55-7.62 (m, 2H), 7.65-7.70 (m, 1H)

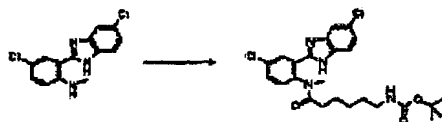
MS (FAB): 445 ( $M^+$ +1, 28 %).

HRMS (FAB): calcd for  $\text{C}_{22}\text{H}_{26}\text{ClN}_4\text{O}_4$  445.1642, Found 445.1651.

(0144)

#### Example 108

tert-butyl 6-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-6-oxohexyl carbamate.



To tetrahydrofuran (30 ml) solution of 6-[(tert butoxycarbonyl) amino] hexanoic acid (1.12 g) and 4-methyl morpholine (1.12 ml) cooled to  $-20^\circ\text{C}$  was added dropwise isopropyl chloroformate (0.855 ml) and was reacted for 40 minutes. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (1.50 g) and triethylamine (2.15 ml) were added to the reaction mixture, and it was reacted at  $25^\circ\text{C}$  for 30 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (300 ml) and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (0.99 g) was obtained as white amorphous solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.34 (s, 9H), 0.96-1.78 (m, 6H), 1.98-2.16 (m, 2H), 2.87 (s, 3H), 2.80-3.02 (m, 2H), 6.65-6.77 (m, 1H), 7.46-8.12 (m, 5H)

MS (FAB): 505 ( $M^+$ +1, 1 %).

HRMS (FAB): calcd for  $\text{C}_{25}\text{H}_{31}\text{Cl}_2\text{N}_4\text{O}_3$  505.1773, Found 505.1757.

(0145)

#### Example 109

6-amino-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylhexane amide

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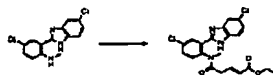
Trifluoroacetic acid (5 ml) was added to tert-butyl 6-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-6-oxohexyl carbamate (800 mg) at 5°C, and produced solution was stirred for one hour. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH7.0 by addition of sodium hydroxide, and extraction was carried out with chloroform (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Produced white solid was recrystallised with hexane / chloroform. Thereby, the title compound (415 mg) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.80-1.35 (m, 8H), 1.70-2.03 (m, 2H), 2.83-2.46 (m, 2H), 3.08 (s, 3H), 7.14-7.18 (m, 1H), 7.54-7.65 (m, 4H), 8.07-8.08(m, 1H).

(0146)

## Example 110

Ethyl (2E)-5-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) methylanilino]-5-oxo-2-pentenoate.



To tetrahydrofuran (110 ml) solution of mono-ethyl (R)-3-acetoxy glutarate (5.80 g) and 4-methyl morpholine (4.86 ml) cooled to -20°C was added dropwise isopropyl chloroformate (3.98 ml) and was reacted for one hour. 4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (6.47 g) and triethylamine (6.16 ml) were added to the reaction mixture, and it was reacted at 25°C for five days. The reaction mixture was transferred to water (300 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (1.83 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.07 (t, J = 7.2 Hz, 1H), 1.13 (t, J = 7.2 Hz, 2H), 2.92-3.02 (m, 2H), 3.04 (s, 2H), 3.12 (s, 1H), 3.90-4.10(m, 2H), 5.58-5.77(m, 1H), 6.43-6.58(m, 0.5H), 6.68-6.80(m, 0.5H), 7.21-8.08(m, 6H)

MS (FAB): 432 (M<sup>+</sup>+1, 42 %).

HRMS (FAB): calcd for C<sub>21</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub> 432.0881, Found 432.0902.

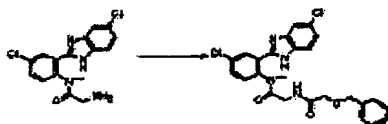
Anal, Calcd for C<sub>21</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>: C, 58.35; H, 4.43; N, 9.72.

Found: C, 58.31; H, 4.57; N, 9.53.

(0147)

## Example 111

2-(benzyloxy)-N-(2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) methylanilino]-2-oxoethyl) acetamide.



Benzyloxy acetyl chloride (689  $\mu$ l) was added dropwise to dichloromethane (30 ml) solution of 2-amino-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (1.27 g) and triethylamine (658  $\mu$ l) cooled to 5°C and was reacted for 20 minutes. The reaction mixture was transferred to saturated aqueous sodium chloride solution (150 ml) and was extracted with chloroform (80 ml x 2), and thereafter was dried with magnesium sulphate, and the recovered organic layer was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (458 mg) was obtained as yellow solid.

mp: 181-184°C

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.00 (s, 3H), 3.46 (dd,  $J$  = 4.8, 16.3 Hz, 1H), 3.73 (dd,  $J$  = 5.2, 16.3 Hz, 1H), 3.90 (s, 2H), 4.53 (s, 2H), 7.23-7.37 (m, 6H), 7.56-7.68 (m, 3H), 7.74 (dd,  $J$  = 2.3, 8.6 Hz, 1H), 7.89 (br, 1H), 8.08 (d,  $J$  = 2.6 Hz, 1H), 13.07 (br, 1H)

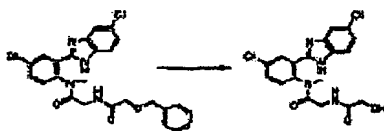
MS (FAB): 497 ( $M^+$ +1, 1 %).

HRMS (FAB): calcd for  $C_{25}H_{23}Cl_2N_4O_3$ , 497.1147, Found 497.1191.

(0148)

## Example 112

N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-2-(glycyl amino)-N-methylacetamide.



At -78°C, boron tribromide (1.23 ml, 1.0M dichloromethane solution) was added dropwise to dichloromethane (30 ml) solution of 2-(benzyloxy)-N-(2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) methylanilino]-2-oxoethyl) acetamide (410 mg). The reaction mixture was transferred to water (200 ml) after having been reacted at -78°C for 15 minutes, and it was adjusted to pH7.0 with potassium hydroxide, and extraction was carried out with chloroform (50 ml x 8). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Thereby, the title compound (244 mg) was obtained as a white solid.

mp: 182°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.97 (s, 3H), 3.46 (dd, J = 4.2, 16.7 Hz, 1H), 3.72 (dd, J = 5.2, 7 Hz, 1H), 3.79 (s, 2H), 7.24-7.28 (m, 1H), 7.58-7.68 (m, 3H), 7.74 (dd, J = 2.6, 8.6 Hz, 1H), 7.87 (br, 1H), 8.08 (d, J = 2.3 Hz, 1H), 13.09 (br, 1H)

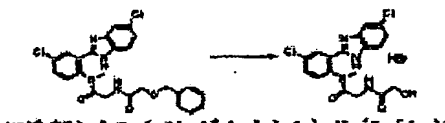
MS (FAB): 407 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>18</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>, 407.0678, Found 407.0648.

(0149)

**Example 113**

N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-2-(glycoyl amino)-N-methylacetamide hydrobromide.



Boron tribromide (9.32 ml, 1.0M dichloromethane solution) was added dropwise to dichloromethane (70 ml) solution of 2-(benzyloxy)-N-{2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) methylanilino]-2-oxoethyl} acetamide (4.56 g) cooled to -78°C and was reacted for 30 minutes. The reaction mixture was transferred to water (400 ml). A produced solid was washed with water and hexane, and it was dried under reduced pressure. Thereby, the title compound (1.32 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.96 (s, 3H), 3.48 (dd, J = 4.2, 16.3 Hz, 1H), 3.69-3.77 (m, 1H), 3.81 (s, 2H), 4.11 (m, 1H), 7.33 (dd, J = 2.0, 8.6 Hz, 1H), 7.65-7.83 (m, 4H), 7.95-8.02 (m, 1H), 8.10 (d, J = 2.3 Hz, 1H)

MS (FAB): 407 (M<sup>+</sup>+1, 48 %).

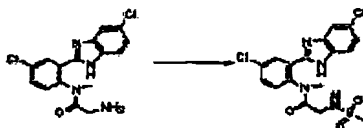
Anal, Calcd for C<sub>18</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub>•0.9HBr: C, 44.65; H, 3.74; N, 11.57.

Found: C, 44.44; H, 4.04; N, 11.52.

(0150)

**Example 114**

N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-2-[(methyl sulphonyl) amino] acetamide.



Methane sulphonyl chloride (35 µl) was added to dichloromethane (5 ml) solution of 2-amino-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (145 mg) and

triethylamine (175  $\mu$ l) and was reacted for one hour. The reaction mixture was transferred to saturated aqueous sodium chloride solution (100 ml) and extraction was carried out with ethyl acetate (50 ml x 2). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was washed with ether and was dried. Thereby, the title compound (129 mg) was obtained as a white solid.

mp: 137°C

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.88 (s, 3H), 2.98 (s, 3H), 3.40-3.63 (m, 2H), 7.19-8.31 (m, 6H)

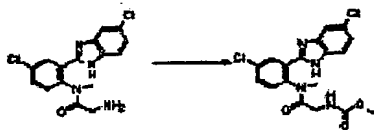
MS (FAB): 427 ( $M^+$ +1, 23 %).

HRMS (FAB): calcd for  $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$  427.0399, Found 427.0402.

(0151)

Example 115

Methyl 2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylanilino]-2-oxoethyl carbamate.



Methyl chloro formate (163  $\mu$ l) was added dropwise to dichloromethane (20 ml) solution of 2-amino-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylacetamide (670 mg) and triethylamine (401  $\mu$ l) cooled to 5°C and was reacted for 30 minutes. The reaction mixture was transferred to water (200 ml), and extraction was carried out with chloroform (60 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Chloroform was added to the residue, and hexane was added. Produced white solid was filtered and was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (580 mg) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.01 (s, 3H), 3.23-3.32 (m, 1H), 3.48 (s, 3H), 3.58 (dd,  $J$  = 6.3, 16.5 Hz, 1H), 7.18-7.33 (m, 2H), 7.59 (d,  $J$  = 8.6 Hz, 1H), 7.56-7.72 (m, 2H), 7.73 (dd,  $J$  = 2.5, 8.6 Hz, 1H), 8.07 (d,  $J$  = 2.5 Hz, 1H), 13.01 (br, 1H)

MS (FAB): 407 ( $M^+$ +1, 100 %).

HRMS (FAB): calcd for  $\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}_3$  407.0678, Found 407.0693.

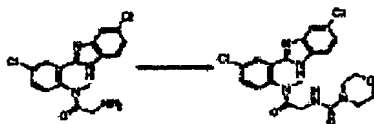
Anal, Calcd for  $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_3 \cdot 0.1\text{H}_2\text{O}$ : C, 52.84; H, 3.97; N, 13.70.

Found: C, 53.13; H, 4.37; N, 13.31.

(0152)

Example 116

N-[2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) anilino]-2-oxoethyl]-4-morpholine carboxamido.



At 10°C, 4-morpholine carbonyl chloride (321  $\mu$ l) was added dropwise to dichloromethane (10 ml) solution of 2-amino-N-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl)phenyl]-N-methylacetamide (740 mg) and triethylamine (591  $\mu$ l) and was reacted for two hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (150 ml) and was extracted with chloroform (100 ml), and thereafter was dried with magnesium sulphate, and the organic layer was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in chloroform, and hexane was added. A produced solid was filtered and was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (924 mg) was obtained as a white solid.

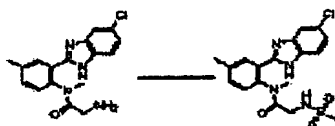
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.85 (s, 1.5H), 2.87 (s, 1.5H), 3.28-3.33(m, 4H), 3.41-6.3(m, 6H), 7.07-7.16(m, 1H), 7.22-7.31(m, 1H), 7.54-7.58(m, 1H), 7.60-7.67(m, 1H), 7.69-7.73 (m, 1H), 8.01 (m, 1H), 13.07 (s, 0.5H), 13.13 (s, 0.5H)

MS (FAB): 462 ( $\text{M}^+ + 1$ , 45 %).

(0153)

#### Example 117

N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methyl-2-[(methylsulphonyl)amino]acetamide.



To dichloromethane (20 ml) solution of 2-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide (640 mg) and triethylamine (540  $\mu$ l) cooled to 5°C, methanesulphonyl chloride (151  $\mu$ l) was added dropwise and was reacted for 18 hours. The reaction mixture was transferred to water (150 ml), and extraction was carried out with chloroform (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (120 mg) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.45 (s, 3H), 2.88 (s, 3H), 2.98 (s, 3H), 3.49-3.53(m, 2H), 03-7.18(m, 1H), 7.19-7.28(m, 1H), 7.42-7.49(m, 2H), 7.55-7.59(m, 2H), 7.81 (br, 1H), 13.02 (br, 1H)

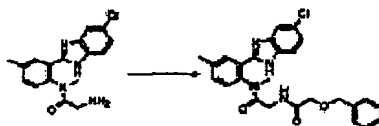
MS (FAB): 407 ( $\text{M}^+ + 1$ , 100 %).

HRMS (FAB): calcd for  $C_{18}H_{20}ClN_2O_3S$  407.0944, Found 407.0955.

(0154)

**Example 118**

2-(benzyloxy)-N-[2-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-2-oxoethyl]  
acetamide.



To dichloromethane (30 ml) solution of 2-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide (1.20 g) and triethylamine (660  $\mu$ l) cooled to 5°C, benzyloxy acetyl chloride (690  $\mu$ l) was added dropwise and was reacted for one hour. The reaction mixture was transferred to water (300 ml), and extraction was carried out with chloroform (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (120 mg) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.48 (s, 3H), 2.98 (s, 3H), 3.46 (dd,  $J = 4.6, 16.8$  Hz, 1H), 7.2 (dd,  $J = 5.1, 16.8$  Hz, 1H), 3.92 (s, 2H), 4.53 (s, 2H), 7.21-7.37 (m, 6H), 7.46 (m, 2H), 7.56-7.61 (m, 2H), 7.81-7.91 (m, 2H), 12.92 (br, 1H)

MS (FAB): 477 ( $M^+ + 1$ , 23 %).

HRMS (FAB): calcd for  $C_{26}H_{26}ClN_4O_3$  477.1693, Found 477.1711.

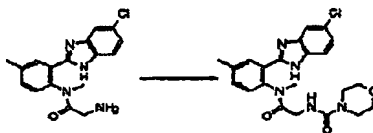
Anal, Calcd for  $C_{26}H_{25}ClN_4O_3 \cdot 0.5\text{H}_2\text{O}$ : C, 64.25; H, 5.40; N, 11.53.

Found: C, 64.26; H, 5.54; N, 11.32.

(0155)

**Example 119**

N-[2-[2-(5-chloro-1H-benzimidazol-2-yl)-4-dimethyl anilino]-2-oxoethyl]-4-morpholine  
carboxamide



To dichloromethane (30 ml) solution of 2-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylacetamide (820 mg) and triethylamine (1.04 ml) cooled to 5°C was added dropwise 4-morpholine carbonyl chloride (291  $\mu$ l) and was reacted for 18 hours. The

reaction mixture was transferred to water (200 ml), and extraction was carried out with chloroform (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was dissolved in chloroform, and hexane was added. A produced solid was filtered and was washed with hexane, and it was dried under reduced pressure. Thereby, the title compound (600 mg) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.43 (s, 3H), 2.83 (s, 3H), 3.23-3.38 (m, 4H), 3.38-3.67 (m, 6H), 7.14-7.78 (m, 6H)

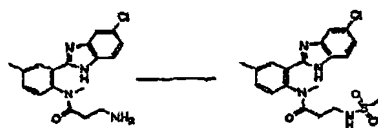
MS (FAB): 442 ( $\text{M}^+ + 1$ , 34 %).

HRMS (FAB): calcd for  $\text{C}_{22}\text{H}_{26}\text{ClN}_5\text{O}_3$  442.1645, Found 442.1667.

(0156)

#### Example 120

N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methyl-3-[(methylsulphonyl)amino]propanamide.



Methanesulphonyl chloride (42  $\mu\text{l}$ ) was added to dichloromethane (8 ml) solution of 3-amino-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methylpropanamide (170 mg) and triethylamine (207  $\mu\text{l}$ ) at  $5^\circ\text{C}$ , and it was reacted for 20 minutes. The reaction mixture was transferred to saturated aqueous sodium chloride solution (100 ml) and extraction was carried out with chloroform (50 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ethyl acetate and was dried under reduced pressure. Thereby, the title compound (120 mg) was obtained as white amorphous solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.13-2.25 (m, 2H), 2.44 (s, 3H), 2.78 (s, 3H), 2.95 (s, 3H), 06-3.13 (m, 2H), 6.82 (br, 1H), 7.24 (dd,  $J = 1.9, 8.6$  Hz, 1H), 7.39 (d,  $J = 8.3$  Hz, 1H), 7.43-7.46 (m, 1H), 7.59 (d,  $J = 8.6$  Hz, 1H), 7.64 (br, 1H), 7.78 (br, 1H), 12.88 (br, 1H)

MS (FAB): 421 ( $\text{M}^+ + 1$ , 42 %).

HRMS (FAB): calcd for  $\text{C}_{19}\text{H}_{22}\text{ClN}_4\text{O}_3\text{S}$  421.1101, Found 421.1118.

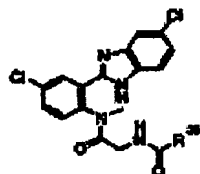
(0157)

In the same way, the following compounds were obtained.



## Examples 121-12

Table 7

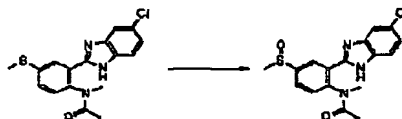


Example	R <sup>2a</sup>	Compound data
121		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 3.00(s, 3H), 3.70(m, J=4.7, 16.6 Hz, 1H), 3.90(d, J=6.5, 16.6 Hz, 1H), 7.26-7.33(m, 1H), 7.55-7.59(m, 2H), 7.25-8.15(m, 3H), 8.62-8.72(m, 1H), 8.85-8.93(m, 1H). MS (FAB): 454(M <sup>+</sup> +1, 35%). HRMS (FAB): calcd for C <sub>22</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>2</sub> 454.0837, found 454.0797.
122		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 3.04(s, 3H), 3.70(m, J=4.7, 16.6 Hz, 1H), 3.96(d, J=6.5, 16.6 Hz, 1H), 7.25-8.17(m, 1H), 7.55-7.59(m, 2H), 7.25-8.15(m, 3H), 8.62-8.72(m, 1H), 8.85-8.93(m, 1H). MS (FAB): 466(M <sup>+</sup> +1, 35%). HRMS (FAB): calcd for C <sub>23</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>2</sub> 466.0789, found 466.0778.
123		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 3.10(s, 3H), 3.95(m, J=5.7, 16.2 Hz, 1H), 3.95(m, J=7.1, 16.2 Hz, 1H), 6.58-6.62(m, 1H), 7.10-7.18(m, 1H), 7.22-7.22(m, 1H), 7.59-7.67(m, 2H), 8.03-8.12(m, 1H), 8.43-8.52(m, 1H). MS (FAB): 443(M <sup>+</sup> +1, 20%). HRMS (FAB): calcd for C <sub>21</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>2</sub> 443.0877, found 443.0855.
124		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 3.03(s, 3H), 3.50(m, J=4.9, 16.2 Hz, 1H), 3.90(m, J=6.1, 16.2 Hz, 1H), 7.11-7.19(m, 1H), 7.21-7.33(m, 1H), 7.55-7.59(m, 2H), 8.06-8.13(m, 1H), 8.52-8.57(m, 1H). MS (FAB): 459(M <sup>+</sup> +1, 35%). HRMS (FAB): calcd for C <sub>23</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>2</sub> 459.0449, found 459.0446.

(0158)

## Example 125

N-[2-(6-chloro-1H-benzimidazol-2-yl)-4-(methylsulfinyl) phenyl]-N-methylacetamide



3-chloro perbenzoic acid (150 mg) was added to dichloromethane (20 ml) solution of N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-(methylsulfinyl) phenyl]-N-methylacetamide (300 mg) at 25°C and it was reacted for 20 minutes. The reaction mixture was transferred to saturated aqueous

sodium chloride solution (150 ml) and extraction was carried out with chloroform (50 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (chloroform / methanol = 50/1). Thereby, the title compound (202 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.66 (s, 3H), 2.88 (s, 3H), 3.03 (s, 3H), 7.21-7.32 (m, 1H), 7.52-7.76 (m, 3H), 7.87-7.91 (m, 1H), 8.23-8.26 (m, 1H)

MS (FAB): 362 (M<sup>+</sup>+1, 10 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>17</sub>ClN<sub>3</sub>O<sub>2</sub>S 362.0729, Found 362.0750.

(0159)

Example 126

(2E)-N-allyl-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-2-butene amide.



At 25°C, crotonyl chloride (527 μl) was added dropwise to pyridine (20 ml) solution of N-allyl-4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) aniline (1.59 g) and was reacted for four hours. The reaction mixture was transferred to water (300 ml), and it was adjusted to pH5.0 with 1N HCl aqueous solution, and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1 to 5/1). Thereby, the title compound (631 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.61 (d, J = 6.9 Hz, 3H), 3.60 (dd, J = 7.6, 14.9 Hz, 1H), 4.69 (dd, J = 5.1, 14.9 Hz, 1H), 4.87-5.00 (m, 2H), 5.58-5.64 (m, 1H), 5.70-5.83 (m, 1H), 6.50-6.63 (m, 1H), 7.24 (dd, J = 1.8, 8.7 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.59-7.68 (m, 3H), 8.07 (d, J = 2.3 Hz, 1H), 12.92 (s, 1H)

MS (EI): 385 (M<sup>+</sup>+24 %).

HRMS (EI): calcd for C<sub>20</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub> 385.0749, Found 385.0739.

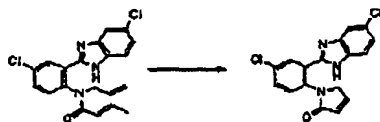
Anal, Calcd for C<sub>20</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O/0.1H<sub>2</sub>O: C, 61.88; H, 4.47; N, 10.83.

Found: C, 61.73; H, 4.48; N, 10.62.

(0160)

Example 127

1-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-1, 5-dihydro-2H-pyrrole-2-one.



At 25°C, benzene (3 ml) solution of (2E)-N-allyl-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-2-butene amide (153 mg) and bis (tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride (16 mg) was stirred for one hour, and thereafter it was reacted at 50°C for three hours. The reaction mixture was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1). Thereby, the title compound (57 mg) was obtained as a slightly grey solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.50 (s, 2H), 6.06-6.09 (m, 1H), 7.17-7.25 (m, 1H), 7.44-48(m, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.49-7.60 (m, 2H), 7.67 (dd, J = 2.5, 8.5 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 12.85 (s, 1H)

MS (FAB): 344 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>3</sub>O 344.0357, Found 344.0374.

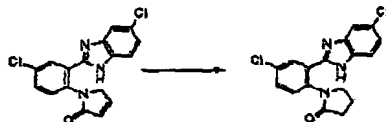
Anal, Calcd for C<sub>17</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O/0.2H<sub>2</sub>O: C, 58.70; H, 3.25; N, 12.08.

Found: C, 58.85; H, 3.30; N, 12.09.

(0161)

#### Example 128

1-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-2-pyrrolidinone.



Sodium borohydride (121 mg) was added to methanol (20 ml) solution of 1-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-1, 5-dihydro-2H-pyrrole-2-on (550 mg) at 25°C, and it was reacted for four hours. The reaction mixture was transferred to water (200 ml), and a produced solid was washed with water, hexane and was dried under reduced pressure. Thereby, the title compound (426 mg) was obtained as a grey solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.09-2.14 (m, 2H), 2.23-2.29 (m, 2H), 3.75 (t, J = 6.8 Hz, 2H), 7.23 (dd, J = 2.0, 8.6 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.54-7.68 (m, 3H), 7.96 (d, J = 2.3 Hz, 1H), 12.91 (br, 1H)

MS (FAB): 346 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>3</sub>O 346.0514, Found 346.0530.

(0162)

## Example 129

(2E)-N-(3-butenyl)-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-butane amide.



trans-crotonyl chloride (726  $\mu$ l) was added dropwise to pyridine (50 ml) solution of N-(3-butenyl)-2-(5-chloro-1H-benzimidazol-2-yl)-4-methylaniline (2.15 g) cooled to 5°C and was reacted for 60 hours. The reaction mixture was transferred to 1N hydrochloric acid aqueous solution (400 ml) and was extracted with ethyl acetate (200 ml), and thereafter was dried with magnesium sulphate, and the organic layer was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (1.55 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.60 (d,  $J = 6.6$  Hz, 3H), 2.12-2.22 (m, 2H), 2.44 (s, 3H), 2.90-98(m, 1H), 4.00-4.12(m, 1H), 4.91-4.99(m, 2H), 5.56-5.78(m, 2H), 6.50-6.62(m, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.21 (dd,  $J = 1.9, 8.6$  Hz, 1H), 7.41 (dd,  $J = 1.3, 7.9$  Hz, 1H), 7.58 (d,  $J = 8.6$  Hz, 1H), 7.60 (m, 1H), 7.81 (d,  $J = 1.3$  Hz, 1H), 12.73 (br, 1H)

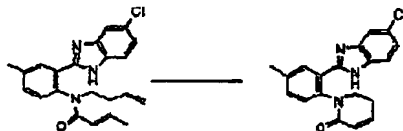
MS (FAB): 380 ( $M^+ + 1$ , 82 %).

HRMS (FAB): calcd for  $\text{C}_{22}\text{H}_{23}\text{ClN}_3\text{O}$  380.1529, Found 380.1501.

(0163)

## Example 130

1-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-5, 6-dihydro-2(1H)-piperidinone.



Bis (tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride (335 mg) was added to toluene (150 ml) solution of (2E)-N-(3-butenyl)-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-butane amide (1.55 g), and it was reacted at 50°C for two hours. The reaction mixture was concentrated, and the residue was dissolved in chloroform, and hexane was added and was crystallised. Thereby, the title compound (1.20 g) was obtained as a grey solid.

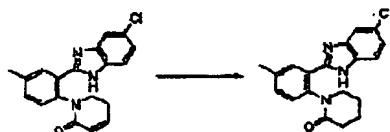
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.29 (s, 3H), 2.50 (br, 2H), 3.79 (br, 2H), 5.68 (d,  $J = 9.9$  Hz, 1H), 6.71 (dt,  $J = 4.3, 9.9$  Hz, 1H), 7.14-7.26 (m, 1H), 7.32 (d,  $J = 8.3$  Hz, 1H), 7.36-7.40 (m, 1H), 7.47-7.65 (m, 3H), 12.74 (br, 1H)

MS (FAB): 338 ( $M^+ + 1$ , 53 %).

HRMS (FAB): calcd for  $\text{C}_{19}\text{H}_{17}\text{ClN}_3\text{O}_3$  38.1060, Found 338.1090.

(0164)

## Example 131

1-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-2-piperidinone.

Sodium borohydride (2.46 g) was added to methanol (80 ml) solution of 1-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-5,6-dihydro-2(1H)-piperidinone (1.10 g) at 25°C, and it was reacted for ten hours. The reaction mixture was transferred to water (400 ml), and extraction was carried out with ethyl acetate (200 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ethyl acetate and was dried under reduced pressure. Thereby, the title compound (810 mg) was obtained as a grey solid.

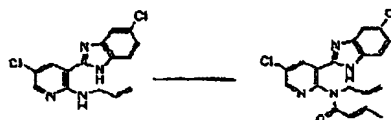
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.80-2.03 (m, 4H), 2.10-2.28 (m, 2H), 2.41 (s, 3H), 5.5-3.67 (m, 2H), 7.17-7.25 (m, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.35-7.38 (m, 1H), 7.48-7.68 (m, 2H), 7.70 (m, 1H), 12.73 (br, 1H)

MS (FAB): 340 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>19</sub>H<sub>19</sub>ClN<sub>3</sub>O 340.1216, Found 340.1215.

(0165)

## Example 132

(2E)-N-allyl-N-[5-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-2-pyridinyl]-2-butene amide.

At 25°C, trans-crotonyl chloride (1.23 ml) was added dropwise to pyridine (50 ml) solution of N-allyl-5-chloro-4-(5-chloro-1H-benzimidazol-2-yl)-2-pyridine amide (3.75 g) and was reacted for 19 hours. The reaction mixture was transferred to 2N hydrochloric acid aqueous solution (250 ml) and was extracted with ethyl acetate (100 ml), and thereafter the organic layer was dried with magnesium sulphate, filtered, and thereafter concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (960 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.46-1.79 (m, 3H), 3.67-4.08 (m, 1H), 4.35-4.72 (m, 1H), 4.86-5.19 (m, 2H), 5.53-5.98 (m, 2H), 6.44-6.58 (m, 1H), 7.26 (dd, J = 1.9, 8.6 Hz, 1H), 7.63 (d, J = 8.6 Hz,

1H), 7.67 (m, 1H), 8.54 (m, 1H), 8.71 (d,  $J = 2.6$  Hz, 1H), 12.95 (br, 1H)

MS (FAB): 387 ( $M^+ + 1$ , 10 %).

HRMS (FAB): calcd for  $C_{19}H_{17}Cl_2N_4O$  387.0779, Found 387.0784.

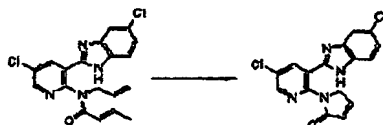
Anal, Calcd for  $C_{19}H_{16}Cl_2N_4O$ : C, 58.93; H, 4.16; N, 14.47.

Found: C, 58.86; H, 4.34; N, 14.49.

(0166)

Example 133

1-[5-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-2-pyridinyl]-1,5-dihydro-2H-pyrrol-2-one.



Bis (tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride (96 mg) was added to dichloromethane (150 ml) solution of (2E)-N-allyl-N-[5-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-2-pyridinyl]-2-butene amide (900 mg) at 25°C, and it was reacted for 48 hours. The reaction mixture was concentrated, and the residue was refined by silica gel column chromatography (chloroform / methanol = 30/1). Thereby, the title compound (588 mg) was obtained as a brown solid.

$^1H$  NMR ( $DMSO-d_6$ ):  $\delta$  4.83 (s, 2H), 6.03-6.07 (m, 1H), 7.17-7.24 (m, 1H), 7.49-7.65 (m, 3H), 8.37 (d,  $J = 2.5$  Hz, 1H), 8.67 (d,  $J = 2.5$  Hz, 1H), 12.81 (s, 1H)

MS (FAB): 345 ( $M^+ + 1$ , 32 %).

HRMS (FAB): calcd for  $C_{16}H_{11}Cl_2N_4O$  345.0309, Found 345.0294.

(0167)

Example 134

1-[5-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-2-pyridinyl]-2-pyrrolidinone.



Sodium borohydride (602 mg) was added to methanol (20 ml) solution of 1-[5-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-2-pyridinyl]-1,5-dihydro-2H-pyrrole-2-on (550 mg) at 25°C, and it was reacted for 40 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with ethyl acetate (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (135 mg, 24 %) was obtained as a

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brown solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.14-2.30 (m, 4H), 4.03-4.08 (m, 2H), 7.16-7.27 (m, 1H), 7.49-7.76 (m, 2H), 8.36 (d,  $J = 2.5$  Hz, 1H), 8.66 (d,  $J = 2.5$  Hz, 1H), 12.86 (br, 1H)

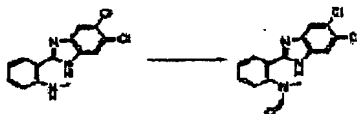
MS (FAB): 347 ( $M^+ + 1$ , 100 %).

HRMS (FAB): calcd for  $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{N}_4\text{O}$  347.0416, Found 347.0457.

(0168)

Example 135

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methyl-formamide.



At 25°C, trimethylsilyl chloride (2.88 ml) was added dropwise with respect to N,N-dimethylformamide (10 ml) solution of triethylamine (3.5 ml) and N,N-dimethylaminopyridine (101 mg). Five minutes later, N,N-dimethylformamide (15 ml) solution of 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (3.0 g) was added dropwise. 12 hours were allowed to pass, and the reaction liquor was poured into saturated aqueous sodium bicarbonate (250 ml). This was extracted with ethyl acetate (200 ml x 3), and the organic layer was washed with water (200 ml x 2) furthermore and next was dried with sodium sulphate. This was concentrated under reduced pressure, and the residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/3) and the title compound (2.65 g) was obtained as a white solid.

mp: 189-190.5°C

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.97 (s, 3H), 7.44-7.68 (m, 3H), 7.86-7.91 (m, 3H), 8.09 (s, 1H), 12.99 (br, 1H).

IR (KBr): 1657, 1577, 1444, 1378, 1359, 1093, 963  $\text{cm}^{-1}$ .

Anal, Calcd for  $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}$ : C, 56.27; H, 3.46; N, 13.12.

Found: C, 56.17; H, 3.66; N, 13.02.

(0169)

Example 136

2-(5-chloro-1H-benzimidazol-2-yl)-4-methoxyphenyl (methyl) formamide.



At 25°C, with respect to N,N-dimethylformamide (5 ml) solution of triethylamine (1.9 ml) and N,N-dimethylaminopyridine (34 mg) was added dropwise trimethylsilyl chloride (0.97 ml). 20

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minutes later, N,N-dimethylformamide (15 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-4-methoxy-N-methylaniline (1.0 g) was added dropwise. 12 hours were allowed to pass, and the reaction liquor was poured into saturated aqueous sodium chloride solution (100 ml). This was extracted with ethyl acetate (150 ml x 3), and the organic layer was washed with water (100 ml x 2) furthermore and next was dried with sodium sulphate. The residue which concentrated this under reduced pressure was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1) and the title compound (753 mg) was obtained as a white solid.

mp: 129-131°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.95 (s, 3H), 3.87 (s, 3H), 7.16-7.26 (m, 2H), 7.41-7.44 (m, 2H), 7.62 (br, 2H), 8.02 (s, 1H), 12.87 (br, 1H).

IR (KBr): 1648, 1505, 1241, 1055, 850 cm<sup>-1</sup>.

(0170)

**Example 137**

2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl (methyl) formamide.



At 25°C, with respect to N,N-dimethylformamide (15 ml) solution of triethylamine (3.77 ml) and N,N-dimethylaminopyridine (108 mg) was added dropwise trimethylsilyl chloride (3.08 ml). 20 minutes later, N,N-dimethylformamide (50 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N, 4-dimethylaniline (3.0 g) was added dropwise. Two days later, the reaction liquor was poured into saturated aqueous sodium chloride solution (200 ml). This was extracted with ethyl acetate (150 ml x 3), and the organic layer was washed furthermore with aqueous sodium chloride (100 ml x 2) and next it was dried with sodium sulphate, and concentration was carried out under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 3/2) and the title compound (1.29 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.42 (s, 3H), 2.96+3.30 (s, 3H), 7.20-7.31 (m, 1H), 36-7.45 (m, 2H), 7.56-7.64 (m, 2H), 7.71-7.74 (m, 1H), 8.05+8.09 (s, 1H), 12.78 (br, 1H).

IR (KBr): 1665, 1502, 927 cm<sup>-1</sup>.

(0171)

**Example 138**

5-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl (methyl) formamide.





At 25°C, trimethylsilyl chloride (2.86 ml) was added dropwise with respect to N,N-dimethylformamide (15 ml) solution of triethylamine (3.51 ml) and N,N-dimethylaminopyridine (100 mg). 30 minutes later, N,N-dimethylformamide (50 ml) solution of 5-chloro-2-(5-chlorobenzimidazol-2-yl)-N-methylaniline (3.0 g) was added dropwise. One day later, the reaction liquor was poured into saturated aqueous sodium chloride solution (200 ml). This was extracted with ethyl acetate (150 ml x 3), and the organic layer was washed furthermore with aqueous sodium chloride (100 ml x 2) and next was dried with sodium sulphate, and concentration was carried out under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1) and the title compound (1.33 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.98 (s, 3H), 7.26 (m, 1H), 7.55-7.74 (m, 4H), 7.90 (m, 1H), 8.09 (s, 1H).

IR (KBr): 1655, 1490, 1414, 820 cm<sup>-1</sup>.

Anal, Calcd for C<sub>15</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>O:

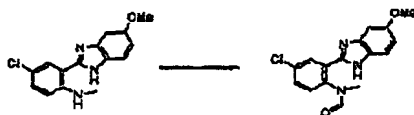
C, 56.27; H, 3.46; N, 13.12.

Found: C, 56.38; H, 3.60; N, 12.86.

(0172)

#### Example 139

4-chloro-2-(5-methoxy-1H-benzimidazol-2-yl) phenyl (methyl) formamide.



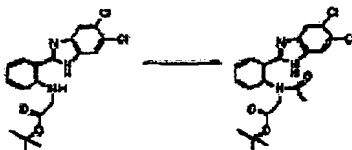
At 25°C, trimethylsilyl chloride (1.94 ml) was added dropwise with respect to N,N-dimethylformamide (10 ml) solution of triethylamine (2.37 ml) and N,N-dimethylaminopyridine (68 mg). 30 minutes later, N,N-dimethylformamide (30 ml) solution of 4-chloro-2-(5-methoxy-1H-benzimidazol-2-yl)-N-methylaniline (2.0 g) was added dropwise. 12 hours were allowed to pass, and the reaction liquor was poured into saturated aqueous sodium bicarbonate (250 ml) and extraction was carried out with ethyl acetate (200 ml x 3). The organic layer was washed with water (200 ml x 2) and next was dried with sodium sulphate. This was concentrated under reduced pressure, and the residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/3) and the title compound (0.52 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.14+3.16 (s, 3H), 3.87 (s, 3H), 6.92-8.38(m, 7H).

IR (KBr): 1688, 1491, 1273, 1160, 1027 cm<sup>-1</sup>.

(0173)

## Example 140

tert-butyl 2-[acetyl-2-(5,6-dichloro-1H-benzimidazol-2-yl) anilino] acetate.

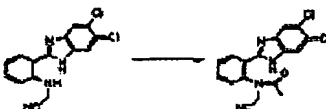
At 25°C, tert-butyl 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) anilino] acetate (500 mg), N,N-dimethylaminopyridine (75 mg) were stirred in acetic anhydride (10 ml) for two days. The solvent was eliminated by distillation and thereafter, was extracted from the ethyl acetate-saturated aqueous sodium bicarbonate. It was concentrated after drying with sodium sulphate. Potassium carbonate (1.76 g) and 2-propanol (20 ml) were added to this, and the mixture was stirred at room temperature for 12 hours. It was extracted from the saturated aqueous sodium chloride solution-acetic acid ethyl ester and was dried with sodium sulphate, and it was concentrated. This solid was recrystallised from tetrahydrofuran-hexane and the title compound (430 mg) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.40 (s, 9H), 1.65 (s, 3H), 3.66 (d, J = 1.7 Hz, 1H), 4.48 (d, J = 1.7 Hz, 1H), 7.59-7.70 (m, 3H), 7.87 (br, 2H), 6.69-7.99 (d, J = 6.9 Hz, 1H), 13.09 (br, 1H).

IR (KBr): 1720, 1677, 1391, 1341, 1154, 778 cm<sup>-1</sup>.

(0174)

## Example 141

N-(cyanomethyl)-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl] acetamide.

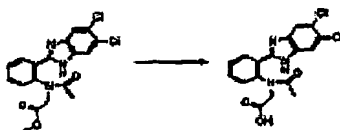
At 25°C, 2-[2-(5,6-dichloro-1H-benzimidazol-2-yl) anilino] acetonitrile (1.48 g), N,N-dimethylaminopyridine (274 mg) were stirred in acetic anhydride (20 ml) for 12 hours. The solvent was eliminated by distillation and thereafter, was extracted from the ethyl acetate-saturated aqueous sodium bicarbonate. It was concentrated after drying with sodium sulphate. Potassium carbonate (1.76 g) and 2-propanol (50 ml) were added to this solid after having been solidified from tetrahydrofuran-hexane, and the mixture was stirred at room temperature for 12 hours. It was extracted from the saturated aqueous sodium chloride solution-acetic acid ethyl ester and was dried with sodium sulphate, and it was concentrated. This solid was recrystallised from tetrahydrofuran-hexane and the title compound (0.93 g) was obtained.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.72 (s, 3H), 4.34 (d,  $J = 17.6$  Hz, 1H), 4.86 (d,  $J = 17.6$  Hz, 1H), 5.8-7.63 (m, 1H), 7.69-7.74 (m, 2H), 7.84 (br, 2H), 8.05-8.08 (m, 1H), 13.32 (br, 1H).

(0175)

## Example 142

2-[acetyl-2-(5,6-dichloro-1H-benzimidazol-2-yl) anilino] acetic acid.



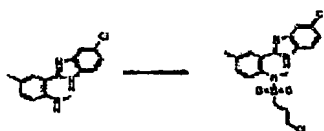
To tetrahydrofuran (15 ml) was added at  $25^\circ\text{C}$ , 2 % sodium hydroxide-methanol solution (20 ml) added to methyl 2-[acetyl-2-(5,6-dichloro-1H-benzimidazol-2-yl) anilino] acetate (350 mg) and the mixture was stirred for 12 hours. 1N-sodium hydroxide solution and ethyl acetate were added, and extraction was carried out. The aqueous layer was acidified with 1N hydrochloric acid, extraction was carried out with ethyl acetate. The oil layer was dried with sodium sulphate, and concentrated. Tetrahydrofuran-cyclohexane was added to an obtained solid, and remaining solid was recovered by filtration and was dried and the title compound (200 mg) was obtained.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.61 (s, 3H), 3.84 (d,  $J = 17.2$  Hz, 1H), 4.54 (d,  $J = 17.2$  Hz, 1H), 6.0-7.67 (m, 3H), 7.86 (br, 2H), 8.02 (d,  $J = 7.0$  Hz, 1H), 13.22 (br, 1H).

(0176)

## Example 143

Synthesis of 3-chloro-N-[2-(5-chloro-1H-benzimidazol-2-yl)-4-methylphenyl]-N-methyl-3-chloropropane sulfonyl amide.



At  $10^\circ\text{C}$ , 3-chloropropane sulphonyl chloride (2.46 ml) was added dropwise with respect to pyridine (50 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-4-methyl-N-methylaniline (5.0 g). It was returned to  $25^\circ\text{C}$ , and it was discharged into saturated aqueous sodium chloride solution after stirring for ten hours, and extraction was carried out with ethyl acetate. The oil layer was washed with saturated aqueous sodium chloride solution (100 ml x 3) and was dried with sodium sulphate, and concentration was carried out under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1) and the title compound (4.0 g) was obtained.

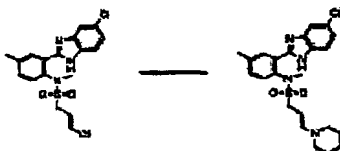
$^1\text{H}$  NMR( $\text{CDCl}_3$ ):  $\delta$  2.38-2.47 (m, 4H), 3.16 (s, 3H), 3.45 (m, 2H), 3.74 (t,  $J = 6.0$  Hz, 2H),

7.26-7.80 (m, 5H), 8.00 (s, 1H), 10.97 (br, 1H).

(0177)

**Example 144**

Synthesis of N-[2-(5-chloro-benzimidazol-2-yl)-4-methylphenyl]-N-methyl-3-(1-piperidino)propane sulphon amide.



N-[2-(5-chloro-benzimidazol-2-yl)-4-methylphenyl]-N-methyl-3-chloropropane sulphonamide (500 mg), piperidine (3.0 ml), xylene (5.0 ml), tetrahydrofuran (2.0 ml) were stirred at 110°C. 12 hours were allowed to pass, and concentration was carried out under reduced pressure, and was refined by silica gel column chromatography (ethyl acetate / triethylamine = 10/1). The title compound (0.43 g) was obtained as a white solid by concentrating under reduced pressure with addition of ethyl acetate-hexane.

<sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.46 (m, 2H), 1.55-1.80 (m, 4H), 2.11(m, 2H), 2.30-2.55(m, 9H), 3.14 (s, 3H), 3.36(m, 2H), 7.24-7.85(m, 5H), 8.00 (s, 1H), 11.09 (br, 1H).

(0178)

**Example 145**

N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methyl methane sulphon amide.



Methane sulphonyl chloride (190 ml) was added to pyridine (10 ml) solution of 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (600 mg) at 25°C, and it was reacted for three days. The reaction mixture was transferred to water (100 ml), and extraction was carried out with ethyl acetate (50 ml x 2). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was washed with ether and was dried. Thereby, the title compound (575 mg) was obtained as a white solid.

mp: 178-182°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.93 (s, 3H), 3.32 (s, 3H), 7.51-7.70 (m, 3H), 7.88 (s, 2H), 7.96 (dd, J = 1.6, 7.6 Hz, 1H)

MS (EI): 369 (M<sup>+</sup>, 11 %).

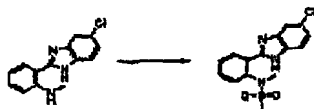
HRMS (EI): calcd for C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S 369.0106, Found 369.0078.

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(0179)

## Example 146

N-[2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-N-methylmethansulphonamide.

At 25°C, methane sulphonyl chloride (980  $\mu$ l) was added dropwise to pyridine (35 ml) solution of 2-(5-chloro-1H-benzimidazol-2-yl)-N-methylaniline (2.51 g) and was reacted for three days. The reaction mixture was transferred to 2N HCl aqueous solution (300 ml) and extraction was carried out with ethyl acetate (100 ml x 2). The organic layer was dried with magnesium sulphate, and vacuum concentration was carried out. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (1.68 g) was obtained as a white solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.92 (s, 3H), 3.31 (s, 3H), 7.22-7.25 (m, 1H), 7.51-7.69 (m, 5H), 7.96 (dd,  $J$  = 1.8, 7.8 Hz, 1H), 12.47 (s, 1H)

MS (EI): 335 ( $M^+$ , 9 %).

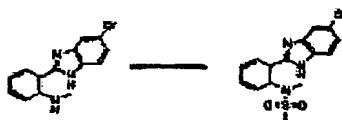
HRMS (EI): calcd for  $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}$  335.0495, Found 335.0472.

Anal, Calcd for  $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}/0.5\text{H}_2\text{O}$ : C, 52.24; H, 4.39; N, 12.18.

Found: C, 52.64; H, 4.30; N, 12.06.

(0180)

## Example 147

N-[2-(6-bromo-1H-benzimidazol-2-yl) phenyl]-N-methyl methane sulphon amide.

At 25°C, methanesulphonyl chloride (1.28 ml) was added dropwise to pyridine (50 ml) solution of 2-(5-bromo-1H-benzimidazol-2-yl)-N-methylaniline (4.17 g) and was reacted for two days. The reaction mixture was transferred to 1N HCl aqueous solution (500 ml), and extraction was carried out with ethyl acetate (200 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with chloroform, and concentration was carried out under reduced pressure. Thereby, the title compound (1.78 g) was obtained as light brown solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.92 (s, 3H), 3.31 (s, 3H), 7.32-7.41 (m, 1H), 6.6 (d,  $J$  = 1.6 Hz, 1H), 7.50-7.69 (m, 3H), 7.74-7.91 (m, 1H), 7.96 (dd,  $J$  = 1.6, 7.2 Hz, 1H), 12.45 (br, 1H)

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MS (EI): 379 (M<sup>+</sup>, 12 %).

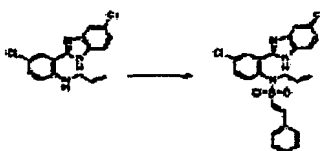
Anal, Calcd for C<sub>15</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>2</sub>S: C, 47.38; H, 3.71; N, 11.05.

Found: C, 47.68; H, 3.80; N, 10.92.

(0181)

**Example 148**

(E)-N-allyl-N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl)phenyl]-2-phenylethane  
sulphonamide.



At 25°C, trans- $\beta$ -styrene sulphonyl chloride (810 mg) was added dropwise to pyridine (20 ml) solution of N-allyl-4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) aniline (1.06 g) and was reacted for 18 hours. The reaction mixture was transferred to water (200 ml), and it was adjusted to pH5.0 with hydrochloric acid, and extraction was carried out with ethyl acetate (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1). Thereby, the title compound (467 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  4.33-4.35 (m, 2H), 5.07-5.17 (m, 2H), 5.93-6.03 (m, 1H), 98 (d, J = 15.2 Hz, 1H), 7.16 (d, J = 15.2 Hz, 1H), 7.21 (dd, J = 1.9, 8.6 Hz, 1H), 7.31-7.44 (m, 6H), 7.50 (d, J = 8.6 Hz, 1H), 7.52-7.61 (m, 1H), 7.63 (dd, J = 2.3, 8.6 Hz, 1H), 7.98 (d, J = 2.3 Hz, 1H), 12.71 (s, 1H)

MS (FAB): 484 (M<sup>+</sup>+1, 8 %).

HRMS (FAB): calcd for C<sub>24</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S 484.0653, Found 484.0622.

Anal, Calcd for C<sub>24</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S: C, 59.51; H, 3.95; N, 8.67.

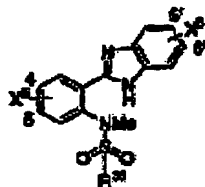
Found: C, 59.44; H, 4.02; N, 8.58.

(0182)

In the same way, following compounds were synthesized.

## Examples 149-157

Table 8



Example	X <sup>a</sup>	X <sup>b</sup>	X <sup>c</sup>	Spectral data
149	H	H	Me	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.00(s, 1H), 7.80(s, 1H), 7.60(s, 1H), 7.40(s, 1H), 7.20(s, 1H), 7.00(s, 1H), 6.80(s, 1H), 6.60(s, 1H), 6.40(s, 1H), 6.20(s, 1H), 6.00(s, 1H), 5.80(s, 1H), 5.60(s, 1H), 5.40(s, 1H), 5.20(s, 1H), 5.00(s, 1H), 4.80(s, 1H), 4.60(s, 1H), 4.40(s, 1H), 4.20(s, 1H), 4.00(s, 1H), 3.80(s, 1H), 3.60(s, 1H), 3.40(s, 1H), 3.20(s, 1H), 3.00(s, 1H), 2.80(s, 1H), 2.60(s, 1H), 2.40(s, 1H), 2.20(s, 1H), 2.00(s, 1H), 1.80(s, 1H), 1.60(s, 1H), 1.40(s, 1H), 1.20(s, 1H), 1.00(s, 1H), 0.80(s, 1H), 0.60(s, 1H), 0.40(s, 1H), 0.20(s, 1H). MS(ESI): m/z (rel. int.): 437.0000.
150	H	H	CH <sub>2</sub> CH <sub>3</sub>	mp: 170-175°C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.00(s, 1H), 7.80(s, 1H), 7.60(s, 1H), 7.40(s, 1H), 7.20(s, 1H), 7.00(s, 1H), 6.80(s, 1H), 6.60(s, 1H), 6.40(s, 1H), 6.20(s, 1H), 6.00(s, 1H), 5.80(s, 1H), 5.60(s, 1H), 5.40(s, 1H), 5.20(s, 1H), 5.00(s, 1H), 4.80(s, 1H), 4.60(s, 1H), 4.40(s, 1H), 4.20(s, 1H), 4.00(s, 1H), 3.80(s, 1H), 3.60(s, 1H), 3.40(s, 1H), 3.20(s, 1H), 3.00(s, 1H), 2.80(s, 1H), 2.60(s, 1H), 2.40(s, 1H), 2.20(s, 1H), 2.00(s, 1H), 1.80(s, 1H), 1.60(s, 1H), 1.40(s, 1H), 1.20(s, 1H), 1.00(s, 1H), 0.80(s, 1H), 0.60(s, 1H), 0.40(s, 1H), 0.20(s, 1H). MS(ESI): m/z (rel. int.): 437.0000. ANAL. Calcd for C <sub>15</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> : C, 58.52%; H, 3.52%; N, 10.21%. Found: C, 58.52%; H, 3.52%; N, 10.21%.
151	H	H	Ph	mp: 167-173°C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.00(s, 1H), 7.80(s, 1H), 7.60(s, 1H), 7.40(s, 1H), 7.20(s, 1H), 7.00(s, 1H), 6.80(s, 1H), 6.60(s, 1H), 6.40(s, 1H), 6.20(s, 1H), 6.00(s, 1H), 5.80(s, 1H), 5.60(s, 1H), 5.40(s, 1H), 5.20(s, 1H), 5.00(s, 1H), 4.80(s, 1H), 4.60(s, 1H), 4.40(s, 1H), 4.20(s, 1H), 4.00(s, 1H), 3.80(s, 1H), 3.60(s, 1H), 3.40(s, 1H), 3.20(s, 1H), 3.00(s, 1H), 2.80(s, 1H), 2.60(s, 1H), 2.40(s, 1H), 2.20(s, 1H), 2.00(s, 1H), 1.80(s, 1H), 1.60(s, 1H), 1.40(s, 1H), 1.20(s, 1H), 1.00(s, 1H), 0.80(s, 1H), 0.60(s, 1H), 0.40(s, 1H), 0.20(s, 1H). ANAL. Calcd for C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> : C, 59.52%; H, 3.52%; N, 10.21%. Found: C, 59.52%; H, 3.52%; N, 10.21%.
152	H	H		mp: 210-220°C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.00(s, 1H), 7.80(s, 1H), 7.60(s, 1H), 7.40(s, 1H), 7.20(s, 1H), 7.00(s, 1H), 6.80(s, 1H), 6.60(s, 1H), 6.40(s, 1H), 6.20(s, 1H), 6.00(s, 1H), 5.80(s, 1H), 5.60(s, 1H), 5.40(s, 1H), 5.20(s, 1H), 5.00(s, 1H), 4.80(s, 1H), 4.60(s, 1H), 4.40(s, 1H), 4.20(s, 1H), 4.00(s, 1H), 3.80(s, 1H), 3.60(s, 1H), 3.40(s, 1H), 3.20(s, 1H), 3.00(s, 1H), 2.80(s, 1H), 2.60(s, 1H), 2.40(s, 1H), 2.20(s, 1H), 2.00(s, 1H), 1.80(s, 1H), 1.60(s, 1H), 1.40(s, 1H), 1.20(s, 1H), 1.00(s, 1H), 0.80(s, 1H), 0.60(s, 1H), 0.40(s, 1H), 0.20(s, 1H). ANAL. Calcd for C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> : C, 59.52%; H, 3.52%; N, 10.21%. Found: C, 59.52%; H, 3.52%; N, 10.21%.

(0183)

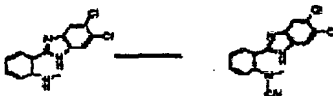
**Table 9**

153	4-Cl	5'-Cl	Me	$^1\text{H NMR}$ (DMSO- $d_6$ ): $\delta$ 2.94(s, 3H), 3.31(s, 3H), 7.25m, 1H, 7.39-7.74(m, 4H), 8.01(s, 2H), 11.0, 11.84D(s, 1H).
154	4-Cl	5'-Cl	Et	$M_p$ 201-202°C. $^1\text{H NMR}$ (DMSO- $d_6$ ): $\delta$ 1.05(t, 3H), 2.26(s, 2H), 2.65(s, 1H), 7.29(s, 1H), 7.39-7.73 (m, 4H), 7.87-7.93 (m, 2H), 7.93-8.00 (m, 2H), 12.00(s, 1H), 12.43, 12.62, 12.95, 13.04, 13.06, 13.7, 13.8, 13.9, 7.75, 7.78, 7.82, 7.83, 7.84, 7.85, 7.86, 7.87, 7.88, 7.89, 7.90, 7.91, 7.92, 7.93, 7.94, 7.95, 7.96, 7.97, 7.98, 7.99, 8.00, 8.01, 8.02, 8.03, 8.04, 8.05, 8.06, 8.07, 8.08, 8.09, 8.10, 8.11, 8.12, 8.13, 8.14, 8.15, 8.16, 8.17, 8.18, 8.19, 8.20, 8.21, 8.22, 8.23, 8.24, 8.25, 8.26, 8.27, 8.28, 8.29, 8.30, 8.31, 8.32, 8.33, 8.34, 8.35, 8.36, 8.37, 8.38, 8.39, 8.40, 8.41, 8.42, 8.43, 8.44, 8.45, 8.46, 8.47, 8.48, 8.49, 8.50, 8.51, 8.52, 8.53, 8.54, 8.55, 8.56, 8.57, 8.58, 8.59, 8.60, 8.61, 8.62, 8.63, 8.64, 8.65, 8.66, 8.67, 8.68, 8.69, 8.70, 8.71, 8.72, 8.73, 8.74, 8.75, 8.76, 8.77, 8.78, 8.79, 8.80, 8.81, 8.82, 8.83, 8.84, 8.85, 8.86, 8.87, 8.88, 8.89, 8.90, 8.91, 8.92, 8.93, 8.94, 8.95, 8.96, 8.97, 8.98, 8.99, 9.00, 9.01, 9.02, 9.03, 9.04, 9.05, 9.06, 9.07, 9.08, 9.09, 9.10, 9.11, 9.12, 9.13, 9.14, 9.15, 9.16, 9.17, 9.18, 9.19, 9.20, 9.21, 9.22, 9.23, 9.24, 9.25, 9.26, 9.27, 9.28, 9.29, 9.30, 9.31, 9.32, 9.33, 9.34, 9.35, 9.36, 9.37, 9.38, 9.39, 9.40, 9.41, 9.42, 9.43, 9.44, 9.45, 9.46, 9.47, 9.48, 9.49, 9.50, 9.51, 9.52, 9.53, 9.54, 9.55, 9.56, 9.57, 9.58, 9.59, 9.60, 9.61, 9.62, 9.63, 9.64, 9.65, 9.66, 9.67, 9.68, 9.69, 9.70, 9.71, 9.72, 9.73, 9.74, 9.75, 9.76, 9.77, 9.78, 9.79, 9.80, 9.81, 9.82, 9.83, 9.84, 9.85, 9.86, 9.87, 9.88, 9.89, 9.90, 9.91, 9.92, 9.93, 9.94, 9.95, 9.96, 9.97, 9.98, 9.99, 10.00, 10.01, 10.02, 10.03, 10.04, 10.05, 10.06, 10.07, 10.08, 10.09, 10.10, 10.11, 10.12, 10.13, 10.14, 10.15, 10.16, 10.17, 10.18, 10.19, 10.20, 10.21, 10.22, 10.23, 10.24, 10.25, 10.26, 10.27, 10.28, 10.29, 10.30, 10.31, 10.32, 10.33, 10.34, 10.35, 10.36, 10.37, 10.38, 10.39, 10.40, 10.41, 10.42, 10.43, 10.44, 10.45, 10.46, 10.47, 10.48, 10.49, 10.50, 10.51, 10.52, 10.53, 10.54, 10.55, 10.56, 10.57, 10.58, 10.59, 10.60, 10.61, 10.62, 10.63, 10.64, 10.65, 10.66, 10.67, 10.68, 10.69, 10.70, 10.71, 10.72, 10.73, 10.74, 10.75, 10.76, 10.77, 10.78, 10.79, 10.80, 10.81, 10.82, 10.83, 10.84, 10.85, 10.86, 10.87, 10.88, 10.89, 10.90, 10.91, 10.92, 10.93, 10.94, 10.95, 10.96, 10.97, 10.98, 10.99, 11.00, 11.01, 11.02, 11.03, 11.04, 11.05, 11.06, 11.07, 11.08, 11.09, 11.10, 11.11, 11.12, 11.13, 11.14, 11.15, 11.16, 11.17, 11.18, 11.19, 11.20, 11.21, 11.22, 11.23, 11.24, 11.25, 11.26, 11.27, 11.28, 11.29, 11.30, 11.31, 11.32, 11.33, 11.34, 11.35, 11.36, 11.37, 11.38, 11.39, 11.40, 11.41, 11.42, 11.43, 11.44, 11.45, 11.46, 11.47, 11.48, 11.49, 11.50, 11.51, 11.52, 11.53, 11.54, 11.55, 11.56, 11.57, 11.58, 11.59, 11.60, 11.61, 11.62, 11.63, 11.64, 11.65, 11.66, 11.67, 11.68, 11.69, 11.70, 11.71, 11.72, 11.73, 11.74, 11.75, 11.76, 11.77, 11.78, 11.79, 11.80, 11.81, 11.82, 11.83, 11.84, 11.85, 11.86, 11.87, 11.88, 11.89, 11.90, 11.91, 11.92, 11.93, 11.94, 11.95, 11.96, 11.97, 11.98, 11.99, 12.00, 12.01, 12.02, 12.03, 12.04, 12.05, 12.06, 12.07, 12.08, 12.09, 12.10, 12.11, 12.12, 12.13, 12.14, 12.15, 12.16, 12.17, 12.18, 12.19, 12.20, 12.21, 12.22, 12.23, 12.24, 12.25, 12.26, 12.27, 12.28, 12.29, 12.30, 12.31, 12.32, 12.33, 12.34, 12.35, 12.36, 12.37, 12.38, 12.39, 12.40, 12.41, 12.42, 12.43, 12.44, 12.45, 12.46, 12.47, 12.48, 12.49, 12.50, 12.51, 12.52, 12.53, 12.54, 12.55, 12.56, 12.57, 12.58, 12.59, 12.60, 12.61, 12.62, 12.63, 12.64, 12.65, 12.66, 12.67, 12.68, 12.69, 12.70, 12.71, 12.72, 12.73, 12.74, 12.75, 12.76, 12.77, 12.78, 12.79, 12.80, 12.81, 12.82, 12.83, 12.84, 12.85, 12.86, 12.87, 12.88, 12.89, 12.90, 12.91, 12.92, 12.93, 12.94, 12.95, 12.96, 12.97, 12.98, 12.99, 13.00, 13.01, 13.02, 13.03, 13.04, 13.05, 13.06, 13.07, 13.08, 13.09, 13.10, 13.11, 13.12, 13.13, 13.14, 13.15, 13.16, 13.17, 13.18, 13.19, 13.20, 13.21, 13.22, 13.23, 13.24, 13.25, 13.26, 13.27, 13.28, 13.29, 13.30, 13.31, 13.32, 13.33, 13.34, 13.35,

(0184)

### Example 158

2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl (methyl) cyan amide.



Cyanidation bromine (439 mg) was added to ethanol (40 ml) solution of 2-(5,6-dichloro-1H-benzimidazol-2-yl)-N-methylaniline (1.01 g) and while heating under reflux, it was reacted for six hours. It was cooled to 25°C and the produced solid was filtered, washed with ether and drying was carried out, and thereby the title compound (310 mg) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.83 (s, 3H), 7.53-7.59 (m, 1H), 7.80-7.88 (m, 2H), 8.26 (s, 1H), 8.43-8.46 (m, 1H), 8.89 (s, 1H).

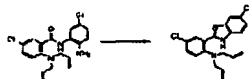
MS (EI): 316 (M<sup>+</sup>, 100 %).

HRMS (EI): calcd for  $C_{15}H_{10}Cl_2N_4$  316.0282, 316.0258.

(0185)

### Example 159

N,N-diallyl-4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) aniline.





Acetic acid (80 ml) liquid of N-(2-amino-5-chlorophenyl)-2-(diallyl amino) benzamide (7.7 g) was stirred at 80°C for five hours. Following cooling to 25°C, it was concentrated. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1). Thereby, the title compound (7.28 g) was obtained as orange oil.

mp: 99°C

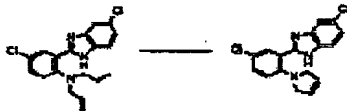
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.58-3.61 (m, 4H), 5.03-5.13 (m, 4H), 5.73-5.88 (m, 2H), 7.18-7.27 (m, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 2.6, 8.6 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 1.9 Hz, 1H), 8.10 (d, J = 2.6 Hz, 1H), 12.67 (m, 1H)

MS (EI): 357 (M<sup>+</sup>, 22 %).

(0186)

Example 160

5-chloro-2-[5-chloro-2-(2,5-dihydro-1H-pyrrol-1-yl) phenyl]-1H-benzimidazole.



At 25°C, dichloromethane (700 ml) solution of N,N-diallyl-4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) aniline (7.28 g) and bis (tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride (839 mg) was stirred for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1). Thereby, the title compound (5.76 g) was obtained as a slightly grey solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.76 (s, 4H), 5.81 (s, 2H), 6.89 (d, J = 8.9 Hz, 1H), 7.23 (dd, J = 2.0, 8.6 Hz, 1H), 7.35-7.41 (m, 2H), 7.48-7.73 (m, 2H), 12.89 (s, 1H)

MS (EI): 329 (M<sup>+</sup>, 100 %).

HRMS (EI): calcd for C<sub>17</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub> 329.0487, Found 329.0466.

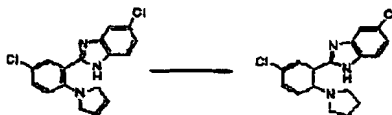
Anal, Calcd for C<sub>17</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>·0.7H<sub>2</sub>O: C, 59.55; H, 4.24; N, 12.26.

Found: C, 59.20; H, 4.24; N, 11.92.

(0187)

Example 161

5-chloro-2-[5-chloro-2-(1-pyrrolidinyl) phenyl]-1H-benzimidazole.



Ethanol (20 ml) solution of 5-chloro-2-[5-chloro-2-(2,5-dihydro-1H-pyrrol-1-yl) phenyl]-1H-benzimidazole (570 mg) and 10% Pd/C (100 mg) was stirred under hydrogen for one hour. The

reaction mixture was filtered by passing through celite, and the filtrate was concentrated under reduced pressure. Thereby, the title compound (373 mg) was obtained as light green colour solid.

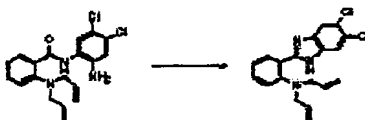
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.74-1.82 (m, 4H), 2.85-3.01 (m, 4H), 9.9 (d, J = 8.9 Hz, 1H), 7.34 (dd, J = 1.8, 8.6 Hz, 1H), 7.42 (dd, J = 2.6, 8.9 Hz, 1H), 7.53 (d, J = 2.6 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H).

MS (FAB+): 332 (M<sup>+</sup>+1, 100 %).

(0188)

**Example 162**

N,N-diallyl-2-(5,6-dichloro-1H-benzimidazol-2-yl) aniline.



Acetic acid (250 ml) liquid of N-(2-amino-4,5-dichlorophenyl)-2-(diallyl amino) benzamide (28.28 g) was stirred at 80°C for one hour. Following cooling to 25°C, it was concentrated. The residue was recrystallised from 2-propanol, and the title compound (22.86 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.58 (s, 2H), 3.06 (s, 2H), 5.02-5.13(m, 4H), 5.74-5.88(m, 2H), 7.17-7.23(m, 1H), 7.30-7.33(m, 1H), 7.40-7.46(m, 1H), 7.89 (s, 1H), 7.91 (s, 1H), 8.13 (dd, J = 1.6, 7.9 Hz, 1H), 12.74 (s, 1H)

MS (EI): 357 (M<sup>+</sup>, 18 %).

HRMS (EI): calcd for C<sub>19</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>, 357.0800, Found 357.0777.

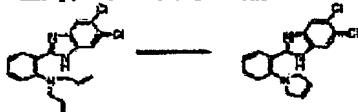
Anal, Calcd for C<sub>19</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>: C, 63.70; H, 4.78; N, 11.73.

Found: C, 63.40; H, 4.83; N, 11.51.

(0189)

**Example 163**

5,6-dichloro-2-[2-(2,5-dihydro-1H-pyrrole-1-yl) phenyl]-1H-benzimidazole.



At 25°C, dichloromethane (100 ml) solution of N,N-diallyl-2-(5,6-dichloro-1H-benzimidazol-2-yl) aniline (560 mg) and bis (tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride (321 mg) was stirred for two hours. The reaction mixture was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (413 mg) was obtained as a slightly grey solid.

mp: 218-223°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.77 (s, 4H), 5.82 (s, 2H), 6.78-6.84 (m, 1H), 6.89-6.92 (m, 1H), 7.34-7.40 (m, 2H), 7.71 (s, 1H), 7.91 (s, 1H), 12.94 (s, 1H)

MS (EI): 329 (M<sup>+</sup>, 100 %).

HRMS (EI): calcd for C<sub>17</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub> 329.0487, Found 329.0503.

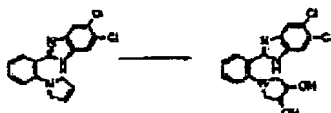
Anal, Calcd for C<sub>17</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>•0.1H<sub>2</sub>O: C, 61.49; H, 4.01; N, 12.65.

Found: C, 61.48; H, 4.24; N, 12.29.

(0190)

**Example 164**

1-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-3,4-pyrrolidine diol.



To tetrahydrofuran (5 ml) of 5,6-dichloro-2-[2-(2,5-dihydro-1H-pyrrole-1-yl) phenyl]-1H-benzimidazole (210 mg) and 4-methyl morpholine N-oxide (78 mg), tert-butanol (5 ml), water (1 ml) and acetone (5 ml) solution was added osmium tetroxide (800 μl, 4 % aqueous solution) at 25°C, and it was reacted for 30 minutes. The reaction mixture was transferred to 10 % sodium bisulphite water (100 ml) and extraction was carried out with chloroform (30 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ether, and thereafter it was dried under reduced pressure. Thereby, the title compound (198 mg) was obtained as a slightly grey solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.84 (dd, J = 4.4, 9.8 Hz, 1H), 3.09 (dd, J = 5.2, 9.8 Hz, 1H), 3.96 (s, 1H), 3.97 (s, 1H), 4.78 (d, J = 4.4 Hz, 2H), 6.79-6.88 (m, 2H), 7.30-7.37 (m, 1H), 7.43 (dd, J = 5.2, 9.8 Hz, 1H), 7.70 (br, 1H), 7.88 (br, 1H), 12.82 (s, 1H)

MS (FAB): 364 (M<sup>+</sup>+1, 22 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 364.0620, Found 364.0619.

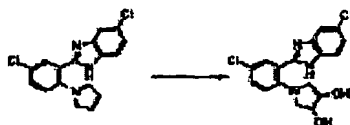
Anal, Calcd for C<sub>17</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: C, 55.23; H, 4.26; N, 11.37.

Found: C, 55.35; H, 4.32; N, 11.23.

(0191)

**Example 165**

1-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-3,4-pyrrolidine diol.



To water (10 ml), tert-butanol (80 ml) and tetrahydrofuran (80 ml) solution of 5-chloro-2-[5-chloro-2-(2,5-dihydro-1H-pyrrole-1-yl) phenyl]-1H-benzimidazole (5.76 g) and 4-methyl morpholine N-oxide (2.14 g) was added osmium tetroxide (2.76 ml, 4 % aqueous solution) and was reacted for 13 hours. The reaction mixture was transferred to 10 % sodium bisulphite water (300 ml), and it was stirred for 30 minutes. Extraction was carried out with ethyl acetate (200 ml). The organic layer was washed with saturated aqueous sodium chloride solution (200 ml x 2), and thereafter was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ether, and thereafter it was dried under reduced pressure. Thereby, the title compound (5.33 g) was obtained as a slightly grey solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.79-2.84 (m, 1H), 3.05-3.10 (m, 1H), 3.95 (s, 2H), 4.80 (br, 2H), 6.85 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 1.9, 8.5 Hz, 1H), 7.35 (dd, J = 2.7, 8.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.55-7.61 (m, 2H), 12.83 (br, 1H)

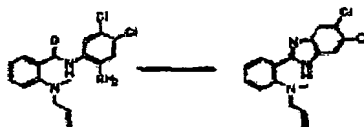
MS (FAB): 364 (M<sup>+</sup>+1, 54 %).

HRMS (FAB): calcd for C<sub>17</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 364.0620, Found 364.0594.

(0192)

#### Example 166

N-allyl-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylamine.



Acetic acid (100 ml) solution of 2-[allyl (methyl) amino]-N-(2-amino-4,5-dichlorophenyl) benzamide (240 mg) was heated to 100°C and stirred for one hour. The reaction solution was cooled to 25°C, and thereafter concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 3/1). Thereby, the title compound (210 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.67 (s, 3H), 3.46 (d, J = 6.2 Hz, 2H), 5.04-5.14 (m, 2H), 5.81-5.91 (m, 1H), 7.14-7.20 (m, 1H), 7.30-7.33 (m, 1H), 7.42-7.48 (m, 1H), 7.87 (s, 2H), 8.04 (dd, J = 1.6, 7.9 Hz, 1H), 12.75 (s, 1H)

MS (FAB): 332 (M<sup>+</sup>+1, 12 %).

Anal, Calcd for C<sub>17</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>:

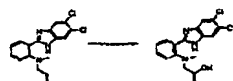
C, 61.46; H, 4.55; N, 12.65.

Found: C, 61.24; H, 4.60; N, 12.55.

(0193)

**Example 167**

3-[2-(5,6-dichloro-1H-benzimidazol-2-yl) (methyl) anilino]-1,2-propanediol.



To water (4 ml), tert-butanol (20 ml) and tetrahydrofuran (20 ml) solution of N-allyl-N-[2-(5,6-dichloro-1H-benzimidazol-2-yl) phenyl]-N-methylamine (1.06 g) and 4-methyl morpholine N-oxide (392 mg) was added osmium tetroxide (506  $\mu$ l, 4 % aqueous solution) at 25°C, and it was reacted for 12 hours. The reaction mixture was transferred to 10 % sodium bisulphite water (150 ml) and extraction was carried out with chloroform (60 ml x 3). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with ether, and thereafter it was dried under reduced pressure. Thereby, the title compound (1.14 g) was obtained as a grey solid.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.62 (s, 3H), 2.87 (dd,  $J$  = 9.9, 12.5 Hz, 1H), 3.10 (dd,  $J$  = 3.6, 5 Hz, 1H), 3.36-3.42 (m, 2H), 3.86-3.98 (m, 1H), 4.88 (br, 1H), 5.69 (br, 1H), 7.25-7.31 (m, 1H), 7.45-7.54 (m, 2H), 7.87 (br, 2H), 8.26 (dd,  $J$  = 1.3, 8.6 Hz, 1H)

MS (FAB): 366 ( $M^+$ +1, 100 %).

HRMS (FAB): calcd for  $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2$  366.0776, Found 366.0789.

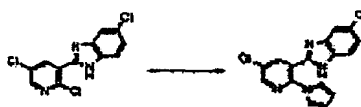
Anal, Calcd for  $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2 \cdot 0.8\text{H}_2\text{O}$ : C, 53.63; H, 4.93; N, 11.04.

Found: C, 53.75; H, 4.69; N, 10.92.

(0194)

**Example 168**

5-chloro-2-[5-chloro-2-(1H-pyrrole-1-yl)-3-pyridinyl]-1H-benzimidazole.



Sodium hydride (2.69 g, 60% in mineral oil) was added to dimethylformamide (20 ml) solution of pyrrole (4.67 ml) cooled to 5°C and was reacted for 30 minutes. 5-chloro-2-(2,5-dichloro-4-pyridinyl)-1H-benzimidazole (2.01 g) was added to the reaction mixture, and mixture thereof was transferred to autoclave, and it was warmed to 100°C and reacted for four hours. After cooling, it was transferred to water (200 ml), and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography

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(hexane / ethyl acetate = 10/1 to 5/1). Thereby, the title compound (1.01 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.11-6.13 (m, 2H), 6.82-6.84 (m, 2H), 7.25-7.32 (m, 1H), 7.60-7.75 (m, 2H), 8.36 (d, J = 2.6 Hz, 1H), 8.73 (d, J = 2.6 Hz, 1H), 12.93 (br, 1H)

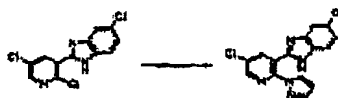
MS (FAB): 329 (M<sup>+</sup>+1, 100 %).

HRMS (FAB): calcd for C<sub>16</sub>H<sub>11</sub>N<sub>4</sub>Cl<sub>2</sub> 329.0360, Found 329.0316.

(0195)

Example 169

5-chloro-2-[(5-chloro-2-(1H-pyrazol-1-yl)-3-pyridinyl)-1H-benzimidazole.



Sodium hydride (1.34 g, 60% in mineral oil) was added to dimethylformamide (25 ml) solution of pyrazole (2.28 g) cooled to 5°C and was reacted for 20 minutes. 5-chloro-2-(2,5-dichloro-4-pyridinyl)-1H-benzimidazole (2.0 g) was added to the reaction mixture, and mixture thereof was transferred to autoclave, and it was warmed to 100°C and reacted for five hours. After cooling, it was transferred to water (200 ml), and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. Thereby, the title compound (552 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.50 (dd, J = 1.7, 2.6 Hz, 1H), 7.22 (dd, J = 2.0, 8.6 Hz, 1H), 5.2 (dd, J = 0.7, 1.7 Hz, 1H), 7.48-7.73 (m, 2H), 8.42 (d, J = 2.6 Hz, 1H), 8.46 (dd, J = 0.7, 2.6 Hz, 1H), 8.75 (d, J = 2.6 Hz, 1H), 12.68 (s, 1H)

MS (FAB): 330 (M<sup>+</sup>+1, 64 %).

HRMS (FAB): calcd for C<sub>15</sub>H<sub>10</sub>N<sub>5</sub>Cl<sub>2</sub> 330.0312, Found 330.0322.

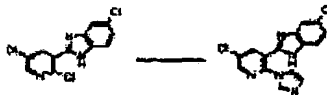
Anal, Calcd for C<sub>15</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>5</sub>: C, 54.57; H, 2.75; N, 21.21.

Found: C, 54.50; H, 2.90; N, 21.19.

(0196)

Example 170

5-chloro-2-[(5-chloro-2-(1H-imidazol-1-yl)-3-pyridinyl)-1H-benzimidazole.



Sodium hydride (1.34 g, 60% in mineral oil) was added to dimethylformamide (25 ml) solution of imidazole (2.28 g) cooled to 5°C and was reacted for 30 minutes. 5-chloro-2-(2,5-dichloro-4-

pyridinyl)-1H-benzimidazole (2.0 g) was added to the reaction mixture, and mixture thereof was transferred to autoclave, and it was warmed to 100°C and reacted for five hours. After cooling, it was transferred to water (200 ml), and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/2). Thereby, the title compound (138 mg) was obtained as white amorphous solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.95 (s, 1H), 7.14 (s, 1H), 7.28 (dd, J = 1.7, 8.6 Hz, 1H), 5.9 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 1.7 Hz, 1H), 7.80 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1H), 13.01 (br, 1H)

MS (FAB): 330 (M<sup>+</sup>+1, 64 %).

HRMS (FAB): calcd for C<sub>15</sub>H<sub>10</sub>N<sub>3</sub>Cl<sub>2</sub> 330.0312, Found 330.0322.

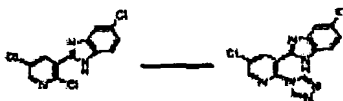
Anal, Calcd for C<sub>15</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>3</sub>: C, 54.57; H, 2.75; N, 21.21.

Found: C, 54.50; H, 2.90; N, 21.19.

(0197)

#### Example 171

5-chloro-2-[5-chloro-2-(4H-1,2,4-triazol-4-yl)-3-pyridinyl]-1H-benzimidazole.



Sodium hydride (1.34 g, 60% in mineral oil) was added to dimethylformamide (25 ml) solution of triazole (2.31 g) cooled to 5°C and was reacted for 30 minutes. 5-chloro-2-(2,5-dichloro-4-pyridinyl)-1H-benzimidazole (2.0 g) was added to the reaction mixture, and mixture thereof was transferred to autoclave, and it was warmed to 100°C and reacted for eight hours. After cooling, it was transferred to water (200 ml), and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (430 mg) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.24 (dd, J = 1.9, 8.6 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 8.57 (d, J = 1.9 Hz, 1H), 8.84 (d, J = 1.9 Hz, 1H), 9.19 (s, 1H), 12.84 (s, 1H)

MS (FAB): 331 (M<sup>+</sup>+1, 43 %).

HRMS (FAB): calcd for C<sub>14</sub>H<sub>8</sub>N<sub>6</sub>Cl<sub>2</sub> 331.0265, Found 331.0274.

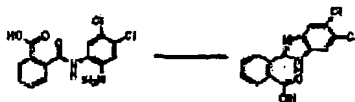
Anal, Calcd for C<sub>14</sub>H<sub>8</sub>N<sub>6</sub>Cl<sub>2</sub>: C, 50.78; H, 2.43; N, 25.38.

Found: C, 50.69; H, 2.67; N, 25.35.



(0198)

## Example 172

2-(5,6-dichloro-1H-benzimidazol-2-yl) benzoic acid.

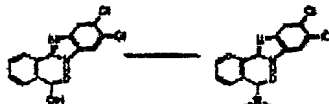
Acetic acid (5 ml) solution of 2-[(2-amino-4,5-dichloro anilino) carbonyl] benzoic acid (180 mg) was heated to 80°C, and it was stirred for four hours. After cooling, precipitated yellow solid was filtered and was washed with hexane, and thereafter, it was dried under reduced pressure and the title compound (165 mg) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.66-7.73 (m, 1H), 7.79-7.85 (m, 1H), 7.94 (s, 1H), 7.91-7.96 (m, 2H), 8.06 (s, 1H)

MS (EI): 288 (M + 18, 100 %).

(0199)

## Example 173

2-(5,6-dichloro-1H-benzimidazol-2-yl)-N,N-dimethylbenzamide.

At 25°C, 2-(5,6-dichloro-1H-benzimidazol-2-yl) benzoic acid (340 mg), dimethylamine hydrochloride (135 mg), 1-(3-dimethylaminopropyl-3-ethyl carbodiimide hydrochloride (360 mg) and dimethylaminopyridine (473 mg) dissolved in dichloromethane (50 ml) solution was stirred for 24 hours. The reaction solution was transferred to saturated aqueous sodium chloride solution (200 ml) and extraction was carried out with chloroform (80 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 1/1). Thereby, the title compound (221 mg) was obtained as a white solid.

mp: 214-217°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.67 (s, 3H), 2.97 (s, 3H), 7.36-7.39 (m, 1H), 7.57-7.61 (m, 2H), 7.83 (s, 2H), 7.94-7.98 (m, 1H), 13.06 (br, 1H)

MS (FAB): 334 (M<sup>+</sup>+1, 64 %).

HRMS (FAB): calcd for C<sub>16</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>3</sub>O 334.0514, Found 334.0524.

Anal, Calcd for C<sub>16</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O•0.2H<sub>2</sub>O: C, 56.88; H, 4.01; N, 12.44.

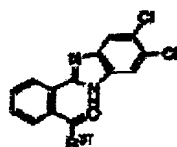
Found: C, 56.83; H, 4.03; N, 12.33.

(0200)

The following compounds were synthesised at similar process.

Examples 174-178

Table 10

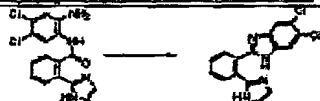


Example	R <sup>3</sup>	Compound data
174		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 1.18-1.22(m, 2H), 1.40-1.67(m, 4H), 3.1-3.18(m, 2H), 3.50-3.69(m, 2H), 7.25-7.39(m, 1H), 7.55-7.52(m, 2H), 7.82(m, 2H), 7.82-7.96(m, 1H).
175		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 1.68-1.96(m, 4H), 3.00-3.15(m, 2H), 3.55(m, 2H), 7.40-7.43(m, 1H), 7.57-7.61(m, 2H), 7.81(m, 2H), 7.89-7.97(m, 1H).
176		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 0.826, J=7.0Hz, 3H, 1.176, J=7.0Hz, 3H, 3.05(m, 3-7.0Hz, 2H), 3.36(m, J=7.0Hz, 2H), 7.37-7.41(m, 1H), 7.58-7.62(m, 2H), 7.76(m, 2H), 7.82-7.86(m, 1H).
177		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 4.38(m, 1H), 4.41(m, 1H), 7.31-7.34(m, 5H), 7.55-7.56(m, 2H), 7.77-7.80(m, 2H), 8.90(m, 1H).
178		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 7.02-7.12(m, 1H), 7.25-7.36(m, 2H), 7.61-7.73(m, 2H), 7.76(m, 2H), 7.85-7.93(m, 1H), 10.41(m, 1H).

実例179

(0201)

Example 179

5,6-dichloro-2-[2-(1H-imidazol-2-yl) phenyl]-1H-benzimidazole.

Using the same process as in Example 172, the title compound was synthesized.

MS (FAB): 329 (M<sup>+</sup>+1, 100 %).HRMS (FAB): calcd for C<sub>16</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>4</sub> 329.0360, Found 329.0347.

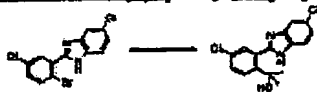
(0202)

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## Example 180

2-[4-chloro-2-(5-chloro-1H-benzimidazol-2-yl) phenyl]-2-propanol.



To tetrahydrofuran (25 ml) solution of 2-(2-bromo-5-chlorophenyl)-5-chloro-1H-benzimidazole (1.51 g) cooled to  $-78^{\circ}\text{C}$  was added dropwise n-butyllithium (1.53M in hexane, 6.30 ml) and was reacted for 15 minutes. Acetone (809  $\mu\text{l}$ ) was added, and stirring was carried out for one hour. The reaction mixture was transferred to saturated aqueous sodium chloride solution (150 ml) and extraction was carried out with ethyl acetate (80 ml). The organic layer was dried with magnesium sulphate, and, after filtration, it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1). Thereby, the title compound (208 mg) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.33 (s, 6H), 7.28 (dd,  $J = 2.0, 8.6$  Hz, 1H), 7.58 (dd,  $J = 2.3, 8.6$  Hz, 1H), 7.65 (d,  $J = 8.6$  Hz, 1H), 7.68-7.74(m, 3H)

MS (EI): 320 ( $M^+$ , 17 %).

Anal, Calcd for  $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O} \cdot 0.2\text{H}_2\text{O}$ : C, 39.16; H, 4.41; N, 8.62.

Found: C, 59.16; H, 4.54; N, 8.51.

(0203)

## Example 181

2-(5,6-dichloro-1H-benzimidazol-2-yl)-N,N-dimethylaniline.



Acetic acid (60 ml) solution of N-(2-amino-4,5-dichlorophenyl)-2-(dimethylamino) benzamide (7.05 g) was heated to  $80^{\circ}\text{C}$ , and it was stirred for 30 minutes. The reaction solution was concentrated, and the residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1) and the title compound (6.05 g) was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.64 (s, 6H), 7.13-7.19 (m, 1H), 7.30-7.32 (m, 1H), 7.42-7.48 (m, 1H), 7.82 (bs, 1H), 7.90 (bs, 1H), 8.07 (dd,  $J = 1.6, 7.6$  Hz, 1H), 12.76 (bs, 1H)

MS (FAB): 306 ( $M^+$ +1, 57 %).

HRMS (EI): calcd for  $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{N}_3$  306.0565, Found 306.0558.

Anal, Calcd for  $\text{C}_{14}\text{H}_{13}\text{Cl}_2\text{N}_3$ : C, 58.84; H, 4.28; N, 13.72.

Found: C, 58.78; H, 4.44; N, 13.56.

(0204)

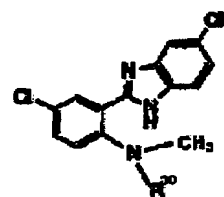
## Example 182

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By a process for the production same as in above-mentioned, it is possible to obtain following compounds 1-609.

Table 11



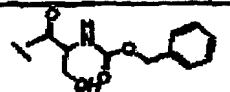
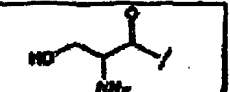



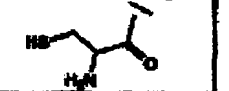
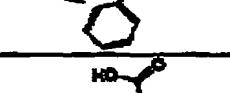

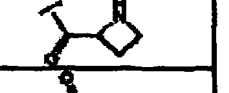

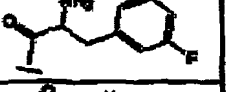





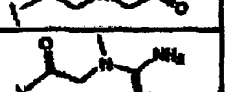






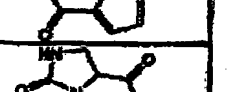

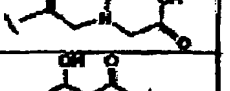

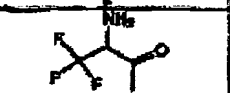
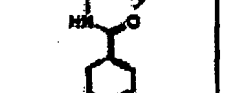
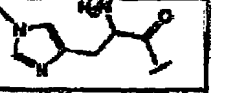
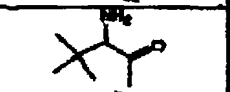

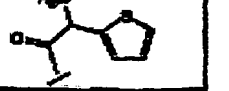


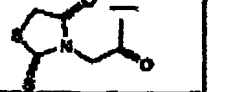
No.	R <sup>30</sup>
1.	
2.	
3.	
4.	
5.	
6.	
7.	

8.	
9.	
10.	
11.	
12.	
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18.	
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21.	
22.	
23.	
24.	
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26.	
27.	
28.	
29.	


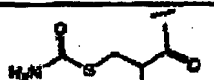











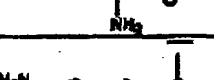

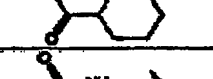

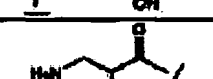









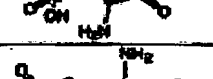




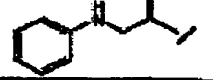





(0205)

Table 12

30.		42.		54.	
31.		43.		55.	
32.		44.		56.	
33.		45.		57.	
34.		46.		58.	
35.		47.		59.	
36.		48.		60.	
37.		49.		61.	
38.		50.		62.	
39.		51.		63.	
40.		52.		64.	
41.		53.		65.	


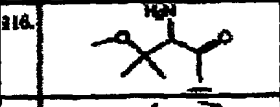
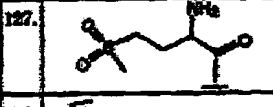


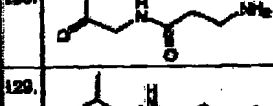
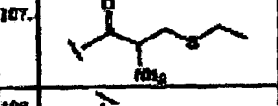
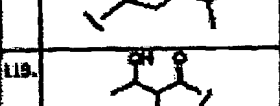
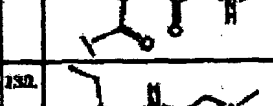

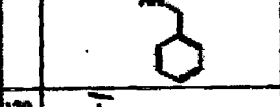
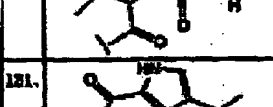

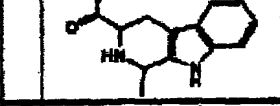
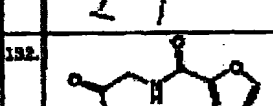
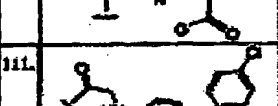
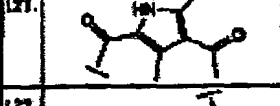
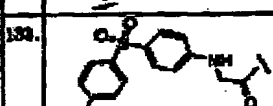
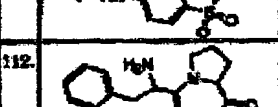
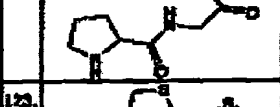
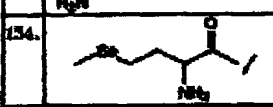
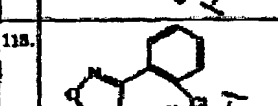

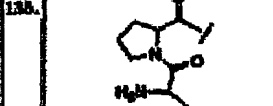
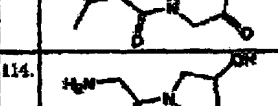
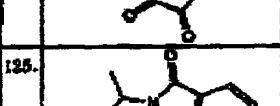
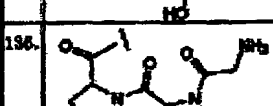

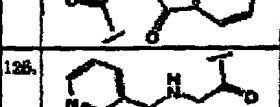
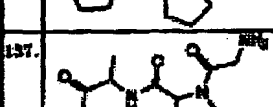

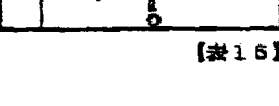
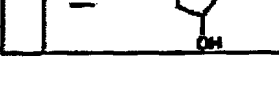
(0206)

Table 13

68.		80.		92.	
69.		81.		93.	
70.		82.		94.	
71.		83.		95.	
72.		84.		96.	
73.		85.		97.	
74.		86.		98.	
75.		87.		99.	
76.		88.		100.	
77.		89.		101.	
78.		90.		102.	
79.		91.		103.	
		92.		104.	

(0207)

Table 14

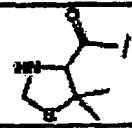
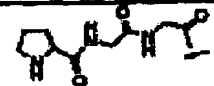

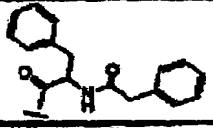

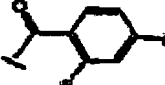
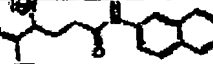
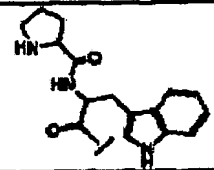


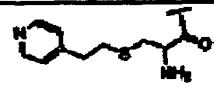
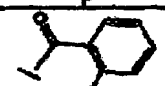
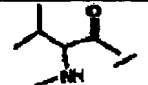
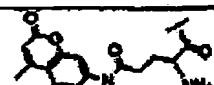


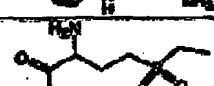

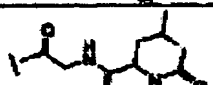


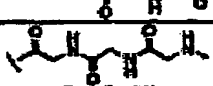


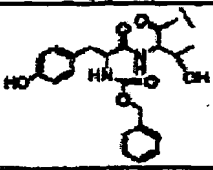


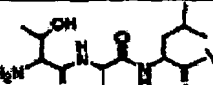


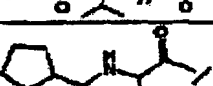
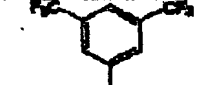

106.		116.		127.	
108.		117.		128.	
107.		118.		129.	
109.		119.		130.	
109.		120.		131.	
110.		121.		132.	
111.		122.		133.	
112.		123.		134.	
113.		124.		135.	
114.		125.		136.	
115.		126.		137.	

【表 15】




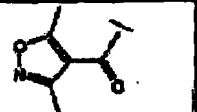
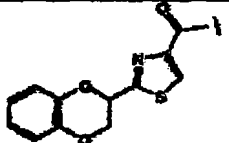

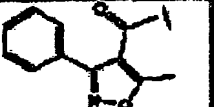
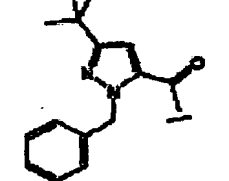


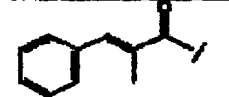


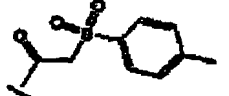
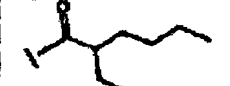

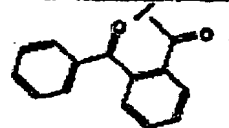


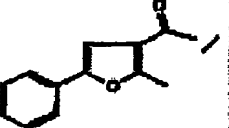

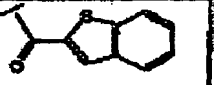
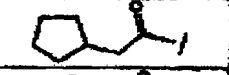




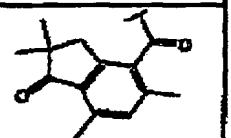
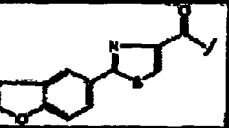

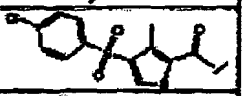
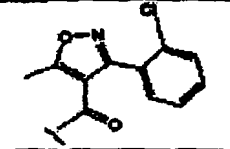
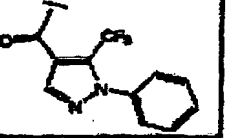

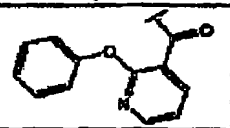
(0208)

Table 15

138.		149.		160.	
139.		150.		161.	
140.		151.		162.	
141.		152.		163.	
142.		153.		164.	
143.		154.		165.	
144.		155.		166.	
145.		156.		167.	
146.		157.		168.	
147.		158.		169.	
148.		159.		170.	

(0209)

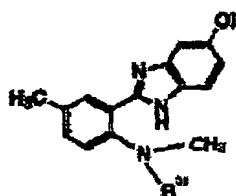
Table 16

171.		184.		195.	
172.		185.		196.	
173.		186.		197.	
174.		187.		198.	
175.		188.		199.	
176.		189.		200.	
177.		190.		201.	
178.		191.		202.	
179.		192.		203.	
180.		193.			
181.		194.			
182.					
183.					

【表 17】

(0210)

Table 17



No	R <sup>n</sup>
204	
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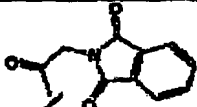
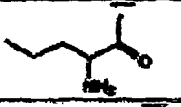
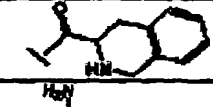

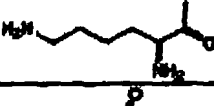
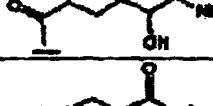



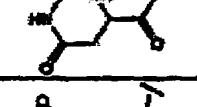
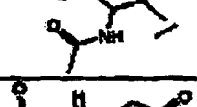
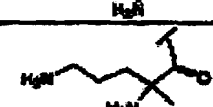



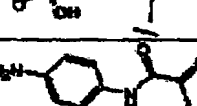
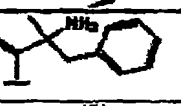

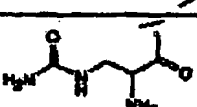


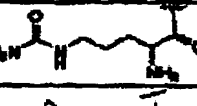


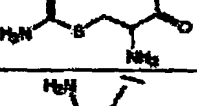


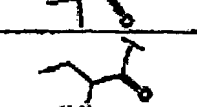
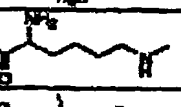

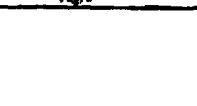

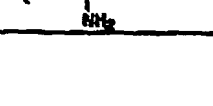


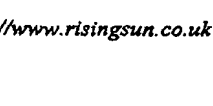


(0211)

Table 18

235		248		261	
236		249		262	
237		250		263	
238		251		264	
239		252		265	
240		253		266	
241		254		267	
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246		259		272	
247		260		273	

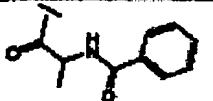
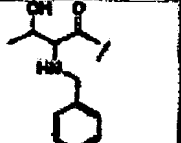
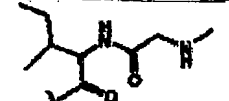

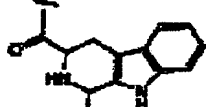

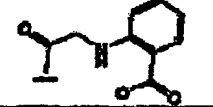

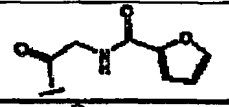
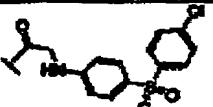
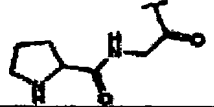
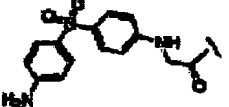

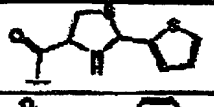
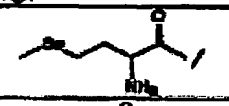
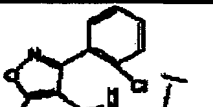
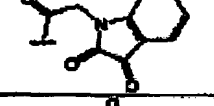
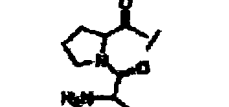

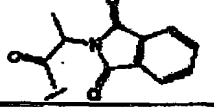

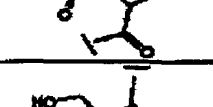
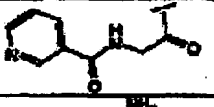
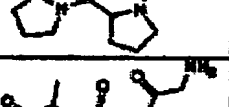
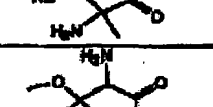
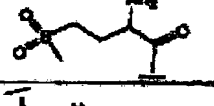
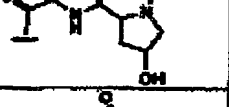
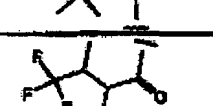
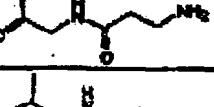
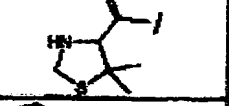
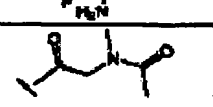

(0212)

Table 19

274		286		298	
275		287		299	
276		288		300	
277		289		301	
278		290		302	
279		291		303	
280		292		304	
281		293		305	
282		294		306	
283		295		307	
284		296		308	
285		297		309	
		298		310	

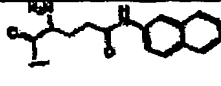
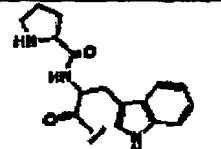
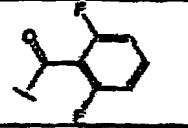


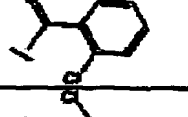


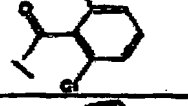


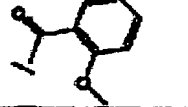
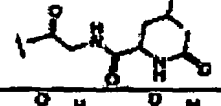
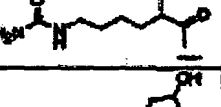
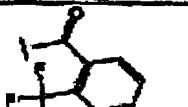
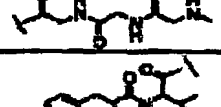
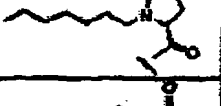
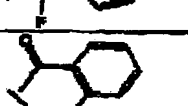
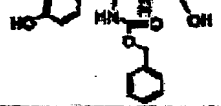

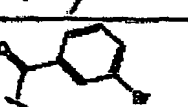
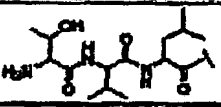
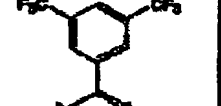
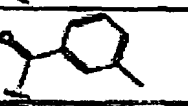
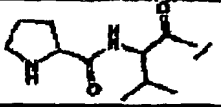
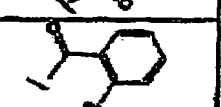
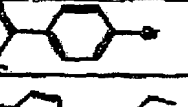
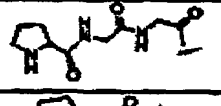
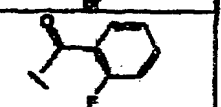
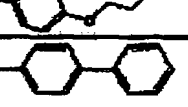
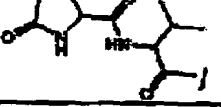

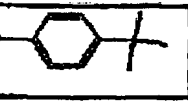

(0213)

Table 20

311		322		333	
312		323		334	
313		324		335	
314		325		336	
315		326		337	
316		327		338	
317		328		339	
318		329		340	
319		330		341	
320		331		342	
321		332			














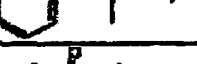




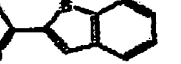




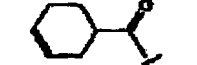






(0214)

Table 21

343		354		365	
344		355		366	
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346		357		368	
347		358		369	
348		359		370	
349		360		371	
350		361		372	
351		362		373	
352		363		374	
353		364		375	
				376	

(0215)

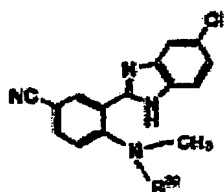
Table 22

377		389		399	
378		390			
379		391		400	
380		392		401	
381		393		402	
382		394		403	
383		395		404	
384		396		405	
385		397		406	
386		398			
387					
388					



(0216)

Table 23



No	R <sup>20</sup>
407	
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432	
433	
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435	
436	
437	

(0217)

Table 24

438		451		464	
439		452		465	
440		453		466	
441		454		467	
442		455		468	
443		456		469	
444		457		470	
445		458		471	
446		459		472	
447		460		473	
448		461		474	
449		462		475	
450		463			

[ 2 5 ]

(0218)

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Table 25

477		489		502	
478		490		503	
479		491		504	
480		492		505	
481		493		506	
482		494		507	
483		495		508	
484		496		509	
485		497		510	
486		498		511	
487		499		512	
488		500		513	
		501			

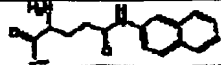
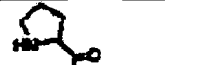






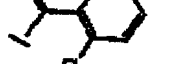












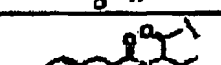





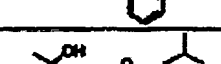


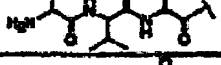



(0219)

Table 26

514		525		536	
515		526		537	
516		527		538	
517		528		539	
518		529		540	
519		530		541	
520		531		542	
521		532		543	
522		533		544	
523		534		545	
524		535			

(0220)

Table 27

545		557		568	
546		558		569	
548		559		570	
549		560		571	
550		561		572	
551		562		573	
552		563		574	
553		564		575	
554		565		576	
555		566		577	
556		567		578	
				579	

(0221)

Table 28



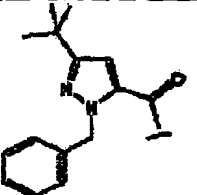



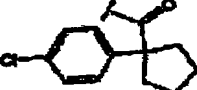















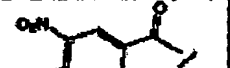



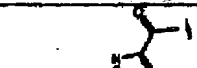



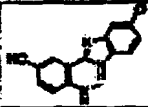
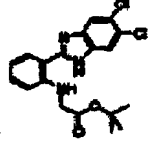
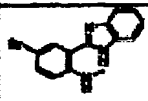
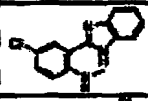
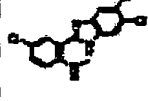
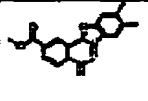
580		592		602	
581		593			
582		594		603	
583		595		604	
584		596		605	
585		597			
586		598		606	
587		599		607	
588		600		608	
589		601		609	
590					
591					

Table 29

Example	Compound	Compound data
2		$^1\text{H}$ NMR ( $\text{CDCl}_3$ ): $\delta$ 8.01(s, 1H), 8.57-8.85(m, 2H), 7.52-7.55(m, 1H), 7.47-7.50(m, 2H), 7.72-7.87(m, 1H), 8.89(br, 1H), 9.55(br, 1H).
3		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 3.70(s, 3H), 4.25(d, J=6.0 Hz, 2H), 6.64(J=6.6 Hz, 1H), 6.77(J=7.2 Hz, 1H), 7.32(J=7.2 Hz, 1H), 7.81(br, 2H), 7.91(J=6.8 Hz, 1H), 8.24(J=6.8 Hz, 1H), 13.10(br, 1H).
4		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 6.82(J=6.6 Hz, 1H), 6.92(J=7.0 Hz, 1H), 7.01(J=7.8 Hz, 1H), 7.46(J=7.1 Hz, 1H), 7.53(br, 2H), 7.98(J=7.1 Hz, 1H), 9.16(J=6.6 Hz, 1H), 13.21(br, 1H).
5		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 2.91(s, 3H), 2.72(s, 1H), 6.72(J=6.0 Hz, 1H), 7.01(J=6.8 Hz, 1H), 7.23(m, 1H), 7.51-7.73(m, 2H), 8.42(br, 1H), 12.91(br, 1H).
6		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 4.85(J=5.1 Hz, 2H), 7.03(m, 1H), 7.28(m, 1H), 7.48(m, 1H), 7.57(m, 1H), 7.72(m, 1H), 8.09(J=2.4 Hz, 1H), 9.28(J=6.8 Hz, 1H), 13.20(J=6.8 Hz, 1H).
7		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 3.69(s, 3H), 4.25(d, J=6.0 Hz, 2H), 6.71(J=6.6 Hz, 1H), 7.25-7.34(m, 2H), 7.63(br, 2H), 8.01(J=6.8 Hz, 1H), 9.43(J=6.8 Hz, 1H), 13.05(br, 1H).
8		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 2.94(d, J=4.9 Hz, 2H), 6.72-6.80(m, 2H), 7.01(J=2.0 Hz, 1H), 7.49-7.70(m, 2H), 7.89 (d, J=8.2 Hz, 1H), 8.08(m, 1H), 12.99(br, 1H).
9		$^1\text{H}$ NMR ( $\text{CDCl}_3$ ): $\delta$ 2.99(s, 3H), 3.82(s, 3H), 5.69(d, J=9.0 Hz, 1H), 6.80-7.70(m, 5H), 8.55(br, 1H).
10		$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): $\delta$ 2.46(s, 3H), 2.92(d, J=4.8 Hz, 2H), 6.77(J=6.6 Hz, 1H), 7.34(m, 1H), 7.56 (m, 1H), 7.80(m, 2H), 7.95(J=6.8 Hz, 1H), 8.89(br, 1H), 12.99(br, 1H).

(0224)

Table 30

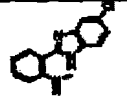
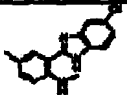
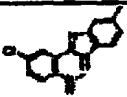
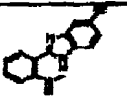
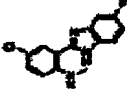

11		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 3.01(d, J=4.9Hz, 2H), 6.89(d, J=8.7Hz, 1H), 7.26(d, J=2.3, 8.7Hz, 1H), 7.56-7.81(m, 3H), 8.34(d, J=2.3Hz, 1H), 9.43(br, 1H), 13.12 (br, 1H).
12		Mp: 188-189°C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 2.65(s, 3H), 6.09(d, J=5.6Hz, 2H), 6.89(d, J=9.0Hz, 1H), 7.25(d, J=1.6, 8.6Hz, 1H), 7.31(d, J=2.3, 9.0Hz, 1H), 7.82 (m, 2H), 8.00(d, J=8.5Hz, 1H), 9.31(m, 1H), 13.09(br, 1H). MS (EI): 391 (M <sup>+</sup> , 23%). HRMS (EI): calcd for C <sub>19</sub> H <sub>15</sub> ClN <sub>3</sub> O, 391.0854, found 391.0894. Anal. Calcd for C <sub>19</sub> H <sub>15</sub> ClN <sub>3</sub> O·0.7H <sub>2</sub> O: C, 55.18; H, 4.10; N, 13.79. Found: C, 55.22; H, 4.24; N, 11.54.
13		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 2.54(d, J=4.9Hz, 2H), 6.78(d, J=8.9Hz, 1H), 7.19-7.27(m, 2H), 7.42(d, J=2.3, 8.5Hz, 1H), 7.73-7.79(m, 1H), 8.11(d, J=2.3Hz, 1H), 9.06-9.12(m, 1H), 12.87(s, 1H). MS (EI): 301 (M <sup>+</sup> , 100%). HRMS (EI): calcd for C <sub>18</sub> H <sub>15</sub> BrN <sub>3</sub> , 301.0214, found 301.0216. Anal. Calcd for C <sub>18</sub> H <sub>15</sub> BrN <sub>3</sub> ·0.1H <sub>2</sub> O: C, 55.31; H, 4.08; N, 13.82. Found: C, 55.20; H, 4.13; N, 13.72.
14		Anal. Calcd for C <sub>18</sub> H <sub>15</sub> ClN <sub>3</sub> : C, 55.25; H, 4.69; N, 16.30. Found: C, 55.14; H, 5.32; N, 16.32.
15		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 2.94(d, J=4.9Hz, 2H), 5.80(d, J=8.1Hz, 1H), 7.38(d, J=2.3, 9.1Hz, 1H), 7.76-7.85(m, 1H), 7.99(d, J=2.5Hz, 1H), 8.78-8.88(m, 1H). MS (EI): 325 (M <sup>+</sup> , 100%). HRMS (EI): calcd for C <sub>18</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>3</sub> , 324.9940, found 324.9923.
16		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) : δ 2.51(s, 3H), 2.33(s, 3H), 3.01 (d, J=4.9Hz, 2H), 3.83(s, 3H), 6.82(d, J=8.7Hz, 1H), 7.88(s, 1H), 7.45(s, 1H), 7.88(d, J=1.9, 8.7Hz, 1H), 8.55(d, J=1.9Hz, 1H), 9.80(m, 1H), 12.82(s, 1H). MS (EI): 329 (M <sup>+</sup> , 100%). HRMS (EI): calcd for C <sub>19</sub> H <sub>15</sub> N <sub>3</sub> O, 329.1477, found 329.1484. Anal. Calcd for C <sub>19</sub> H <sub>15</sub> N <sub>3</sub> O·0.1H <sub>2</sub> O: C, 69.47; H, 6.23; N, 19.60. Found: C, 69.26; H, 6.18; N, 13.16.

122-3-11



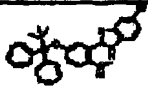

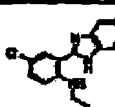
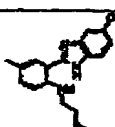
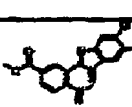
(0225)

Table 31

17		$^1\text{H}$ NMR (DMSO- $d_6$ ): $\delta$ 2.94(d, J=4.5 Hz, 2H), 5.68-6.76(m, 2H), 7.22(dd, J=2.1, 8.3 Hz, 1H), 7.29-7.35(m, 1H), 7.49-7.70(m, 2H), 7.88(dd, J=1.6, 7.9 Hz, 1H), 8.77-8.91(m, 1H), 12.89(br, 1H). MS (EI) 267 ( $M^+$ , 100%). HRMS (EI) calcd for $C_{17}H_{11}ClN$ , 267.0720, found 267.0647.
18		$^1\text{H}$ NMR (DMSO- $d_6$ ): $\delta$ 2.28(s, 3H), 2.91(d, J=4.5 Hz, 2H), 6.89(d, J=6.4 Hz, 1H), 7.15(m, J=1.5, 8.5 Hz, 1H), 7.21(dd, J=1.9, 8.6 Hz, 1H), 7.52-7.82(m, 2H), 7.72(d, J=1.5 Hz, 1H), 8.61(s, 1H), 12.88(br, 1H). MS (EI): 271 ( $M^+$ , 100%). HRMS (EI) calcd for $C_{17}H_{11}ClN$ , 271.0878, found 271.0894. Anal. Calcd for $C_{17}H_{11}ClN$ : C, 66.30; H, 5.19; N, 16.46. Found: C, 66.20; H, 5.07; N, 16.19.
19		$^1\text{H}$ NMR (DMSO- $d_6$ ): $\delta$ 2.33(s, 3H), 2.94(d, J=4.9 Hz, 2H), 5.76(d, J=8.0 Hz, 1H), 7.03-7.05(m, 1H), 7.30(m, J=2.3, 8.0 Hz, 1H), 7.28-7.54(m, 2H), 7.97(d, J=2.3 Hz, 1H), 8.07(s, 1H), 12.71(br, 1H). MS (EI): 271 ( $M^+$ , 100%). HRMS (EI) calcd for $C_{17}H_{11}ClN$ , 271.0878, found 271.0872.
20		$^1\text{H}$ NMR (DMSO- $d_6$ ): $\delta$ 2.91(d, J=4.6 Hz, 2H), 6.71-6.76(m, 1H), 7.29(d, J=8.0 Hz, 1H), 7.23-7.25(m, 1H), 7.39(dd, J=1.2, 8.9 Hz, 1H), 7.55-7.58(m, 1H), 7.79(d, J=1.8 Hz, 1H), 7.81-7.84(m, 1H). MS (EI): 301 ( $M^+$ , 100%). HRMS (EI) calcd for $C_{17}H_{11}BrN$ , 301.0416, found 301.0382.
21		$^1\text{H}$ NMR (DMSO- $d_6$ ): $\delta$ 2.99(d, J=4.8 Hz, 2H), 6.76(d, J=8.2 Hz, 1H), 7.09-7.11(m, 1H), 7.31(dd, J=2.4, 8.9 Hz, 1H), 7.33-7.43(m, 1H), 7.54-7.65(m, 1H), 7.98(d, J=2.6 Hz, 1H), 8.95(s, 1H), 12.98(br, 1H). MS (EI): 275 ( $M^+$ , 100%). HRMS (EI) calcd for $C_{16}H_{11}ClFN$ , 275.0625, found 275.0597. Anal. Calcd for $C_{16}H_{11}ClFN$ : C, 60.99; H, 4.02; N, 15.24. Found: C, 60.94; H, 4.34; N, 15.06.
22		$^1\text{H}$ NMR (DMSO- $d_6$ ): $\delta$ 3.07(d, J=4.9 Hz, 2H), 7.54(br, 1H), 7.85-7.88(m, 2H), 8.32(s, 1H), 12.76(s, 1H). MS (EI): 297 ( $M^+$ , 100%). HRMS (EI) calcd for $C_{17}H_{11}Cl_2N$ , 297.0647, found 297.0616.

(0226)

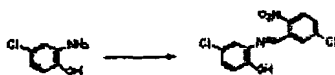
Table 32

23		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 1.07(s, 3H), 2.79(s, 3H), 6.42(d, J=8.9Hz, 1H), 6.49(d, J=2.6, 8.9Hz, 1H), 7.31-7.24(m, 1H), 7.40-7.49(m, 5H), 7.53-7.57(m, 1H), 7.69-7.73(m, 6H), 8.43(br, 1H), 12.93(br, 1H). MS (FAB): 519 (M <sup>+</sup> +1, 64%). HRMS (FAB): calcd for C <sub>29</sub> H <sub>21</sub> ClN <sub>2</sub> O 512.1324, found 512.1329.
24		Mp: 149 °C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.95(d, J=4.0Hz, 1H), 8.67-8.73(m, 1H), 7.5-6.78(m, 1H), 7.15-7.35(m, 2H), 7.27-7.38(m, 1H), 7.49-8.14(m, 1H), 7.69-7.67(m, 1H), 7.90(d, J=1.8, 7.9Hz, 1H), 8.98(m, 1H), 12.71(s, 1H). MS (FAB): 224 (M <sup>+</sup> +1, 100%). HRMS (FAB): calcd for C <sub>19</sub> H <sub>13</sub> N <sub>2</sub> 224.1107, found 224.1102. Anal. Calcd for C <sub>19</sub> H <sub>13</sub> N <sub>2</sub> : C, 75.31; H, 5.87; N, 18.82. Found: C, 75.27; H, 5.88; N, 18.90.
25		Mp: 141-144 °C. <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 3.95-4.02(m, 2H), 5.16-5.21(m, 1H), 5.34(m, 1H), 5.93-6.05(m, 1H), 6.79(d, J=9.1Hz, 1H), 7.24(d, J=1.9, 8.8Hz, 1H), 7.30(d, J=2.6, 8.1Hz, 1H), 7.44-7.16(m, 2H), 8.00(d, J=2.6Hz, 1H), 8.24(d, J=8.6Hz, 1H), 12.90(s, 1H). MS (EI) 317 (M <sup>+</sup> , 100%). HRMS (EI) calcd for C <sub>19</sub> H <sub>13</sub> ClN <sub>2</sub> 317.0487, found 317.0501.
26		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 2.27(s, 3H), 2.89-2.94(m, 2H), 3.25-3.01(m, 2H), 5.10-5.15(m, 1H), 5.21-5.29(m, 1H), 5.93-5.98(m, 1H), 6.72(d, J=8.8Hz, 1H), 7.19(d, J=1.5, 8.2Hz, 1H), 7.21(d, J=5.5, 8.5Hz, 1H), 7.49-7.58(m, 2H), 7.71(d, J=1.5Hz, 1H), 8.79(br, 1H), 12.92(s, 1H). MS (FAB): 312 (M <sup>+</sup> +1, 13%). HRMS (FAB): calcd for C <sub>19</sub> H <sub>13</sub> ClN <sub>2</sub> 312.1267, found 312.1262. Anal. Calcd for C <sub>19</sub> H <sub>13</sub> ClN <sub>2</sub> : C, 69.34; H, 5.82; N, 13.48. Found: C, 69.29; H, 5.85; N, 13.43.
27		<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 3.01(d, J=1.9Hz, 3H), 3.84(s, 3H), 6.85(d, J=8.8Hz, 1H), 7.82(br, 2H), 7.90(d, J=1.8, 8.9Hz, 1H), 8.55(d, J=1.9Hz, 1H), 9.69(m, 1H). Anal. Calcd for C <sub>19</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> •0.6H <sub>2</sub> O: C, 53.49; H, 3.93; N, 11.79. Found: C, 53.83; H, 3.72; N, 11.55.

(0227)

## Reference Example 28

4-chloro-2-((1E)-(5-chloro-2-nitrophenyl) methylidene) amino} phenol.



Cyclohexane (200 ml) solution of 2-amino-4-chlorophenol (7.72 g) and 5-chloro-2-nitrobenzaldehyde (10.0 g) was heated under reflux for five hours. During this procedure, water generated was eliminated using a Dean Stark apparatus. The reaction solution was cooled to 25°C and thereafter, the produced brown solid was filtered, washed with hexane and dried under reduced pressure. Thereby, the title compound (15.4 g) was obtained as a brown solid.

mp: 175-178°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.94 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 2.6, 8.6 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.84 (dd, J = 2.3, 8.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.98 (s, 1H), 9.62 (bs, 1H)

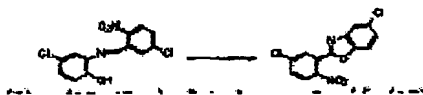
MS (EI): 310 (M<sup>+</sup>, 35 %).

HRMS (EI): calcd for C<sub>13</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>, 309.9912, Found 309.9886.

(0228)

#### Reference Example 29

##### 5-chloro-2-(5-chloro-2-nitrophenyl)-1,3-benzoxazole.



Silver oxide (I) (13.48 g) was added to chloroform (300 ml) solution of 4-chloro-2-(((1E)-(5-chloro-2-nitrophenyl)methylidene)amino)phenol (15.10 g). At 25°C, the reaction mixture was stirred for 18 hours and filtered using celite. The filtrate was concentrated, and the residue was washed with chloroform and next was dried under reduced pressure. Thereby, the title compound (4.14 g) was obtained as a brown solid.

mp: 160-161°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.57 (dd, J = 2.3, 8.9 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 2.3, 8.5 Hz, 1H), 8.02-8.03 (m, 1H), 8.22 (d, J = 8.9 Hz, 1H), 8.26 (d, J = 2.3 Hz, 1H)

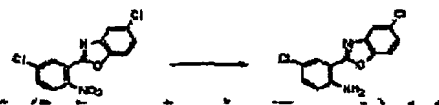
MS (EI): 308 (M<sup>+</sup>, 78 %).

HRMS (EI): calcd for C<sub>13</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>, 307.9755, Found 307.9781.

(0229)

#### Reference Example 30

##### 4-chloro-2-(5-chloro-1,3-benzoxazol-2-yl) aniline.



A mixture of 5-chloro-2-(5-chloro-2-nitrophenyl)-1,3-benzoxazole (4.0 g), iron (3.61 g), ammonium acetate (346 mg), ethanol (30 ml), toluene (30 ml), 1,4-dioxane (30 ml) and water (30 ml) was heated under reflux for three hours. The reaction solution was cooled to 25°C and filtered using celite, and the filtrate was concentrated. Thereby, the title compound (3.21 g) was obtained as light brown solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 6.95 (d, J = 8.9 Hz, 1H), 7.26 (bs, 2H), 7.32 (dd, J = 2.6, 8.9 Hz, 1H), 7.46 (dd, J = 2.1, 8.6 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 2.6 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H)

MS (EI): 278 (M<sup>+</sup>, 100 %).

HRMS (EI): calcd for C<sub>13</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>O 278.0014, Found 278.0021.

(0230)

Reference Example 31

N-(4-chloro-2-(5-chloro-1,3-benzoxazol-2-yl) phenyl) acetamide.



At 25°C, acetyl chloride (105 μl) was added dropwise with respect to dichloromethane (8 ml) solution of 4-chloro-2-(5-chloro-1,3-benzoxazol-2-yl) aniline (274 mg) and pyridine (397 μl). The reaction solution was stirred for ten minutes, and thereafter it was transferred to water (50 ml). Produced white solid was filtered and was washed with hexane and was dried under reduced pressure. Thereby, the title compound (123 mg) was obtained as a white solid.

mp: 215-217°C

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.24 (s, 3H), 7.55 (dd, J = 2.5, 8.9 Hz, 1H), 7.69 (dd, J = 2.5, 9 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 2.5 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.53 (d, J = 8.9 Hz, 1H), 11.27 (s, 1H)

MS (EI): 320 (M<sup>+</sup>, 39 %).

HRMS (EI): calcd for C<sub>15</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> 320.0119, Found 320.0131.

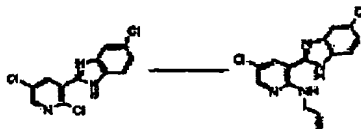
Anal, Calcd for C<sub>15</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 56.10; H, 3.14; N, 8.72.

Found: C, 55.95; H, 3.25; N, 8.66.

(0231)

Reference Example 32

N-allyl-5-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-2-pyridinamine.



A mixture of 5-chloro-2-(2,5-dichloro-4-pyridinyl)-1H-benzimidazole (4.01 g) and allylamine (20.15 ml) was transferred into autoclave, and it was warmed to 110°C and reacted for three hours. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 5/1). Thereby, the title compound (3.78 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.18-4.23 (m, 2H), 5.10-5.16 (m, 1H), 5.22-5.31 (m, 1H), 5.97-6.11 (m, 1H), 7.27 (dd, J = 2.0, 8.6 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.69 (m, 1H), 8.20 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H), 9.59 (t, J = 5.6 Hz, 1H), 13.22 (s, 1H).

Anal, Calcd for C<sub>15</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>4</sub>:

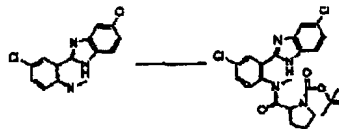
C, 56.44; H, 3.79; N, 17.55.

Found: C, 56.56; H, 4.09; N, 17.47.

(0232)

#### Reference Example 33

2-[allyl (methyl) amino]-N-(2-amino-4,5-dichlorophenyl) benzamide.



At 25°C, 2-[allyl (methyl) amino] benzoic acid (4.72 g), 4,5-dichloro-1,2-phenylenediamine (3.55 g), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (5.68 g) and dimethylaminopyridine (9.05 g) dissolved in chloroform (100 ml) solution were stirred for four hours. The reaction solution was transferred to water (700 ml), and extraction was carried out with chloroform (100 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (2.59 g) was obtained as slightly yellow solid.

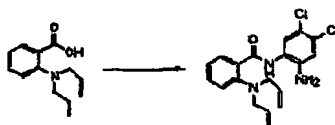
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.70 (s, 3H), 3.62 (d, J = 6.2 Hz, 2H), 5.11-5.14 (m, 1H), 5.23-5.33 (m, 1H), 5.33 (s, 2H), 5.79-5.89 (m, 1H), 6.99 (s, 1H), 7.14-7.19 (m, 1H), 7.28-7.31 (m, 1H), 7.45-7.51 (m, 1H), 7.80 (dd, J = 1.6, 7.6 Hz, 1H), 7.90 (s, 1H), 11.12 (s, 1H)

MS (EI): 349 (M<sup>+</sup>, 13 %).

HRMS (EI): calcd for C<sub>17</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O 349.0749, Found 349.0715.

(0233)

## Reference Example 34

N-(2-amino-4,5-dichlorophenyl)-2-(diallyl amino) benzamide.

The title compound was synthesized using the same process as in Reference Example 33.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.66 (s, 2H), 3.69 (s, 2H), 5.08-5.19(m, 4H), 5.31 (s, 2H), 7.4-5.89(m, 2H), 6.99 (s, 1H), 7.16-7.22(m, 1H), 7.28-7.31(m, 1H), 7.44-7.51 (m, 1H), 7.83 (dd, J = 1.6, 7.6 Hz, 1H), 7.86 (s, 1H), 11.10 (s, 1H)

MS (EI): 375 (M<sup>+</sup>, 8 %).

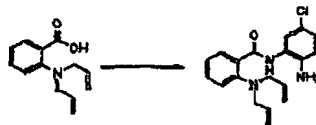
HRMS (EI): calcd for C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O 375.0905, Found 375.0929.

Anal, Calcd for C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O: C, 60.65; H, 5.09; N, 11.17.

Found: C, 60.62; H, 5.07; N, 11.12.

(0234)

## Reference Example 35

N-(2-amino-5-chlorophenyl)-2-(diallyl amino) benzamide.

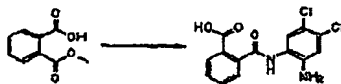
The title compound was synthesized using the same process as in Reference Example 33.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.67-3.70 (m, 4H), 5.09-5.14 (m, 3H), 5.19-5.21 (m, 3H), 7.3-5.88 (m, 2H), 6.62 (dd, J = 2.3, 8.6 Hz, 1H), 6.83 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.49 (dd, J = 2.6, 8.6 Hz, 1H), 7.76 (d, J = 2.6 Hz, 1H), 10.71 (s, 1H)

MS (EI): 341 (M<sup>+</sup>, 12 %).

(0235)

## Reference Example 36

2-[(2-amino-4,5-dichloro anilino) carbonyl] benzoic acid.

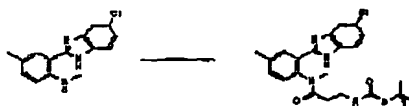
The title compound was synthesized using the same process as in Reference Example 33.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.87 (s, 2H), 6.95 (s, 1H), 7.42 (s, 1H), 7.84-7.96(m, 5H)

MS (EI): 306 (M<sup>+</sup>-18, 100 %).

(0236)

## Reference Example 37

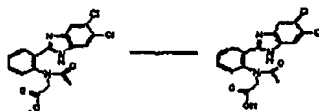
2-(1H-imidazol-2-yl) benzoic acid.

At 25°C, ammonia water (130 ml) was added to 2-carboxybenzaldehyde (25.2 g). At 25°C, glyoxal (50 ml) was added dropwise with respect to this mixture over a period of one hour. The reaction solution was heated to 100°C and stirred for three hours, and it was cooled to 25°C, and thereafter, it was left to stand for 12 hours. The reaction mixture was filtered, and the filtrate was adjusted to pH2.0 with concentrated hydrochloric acid. A produced brown solid was separated by filtration, and washed with water and then ethanol, and was heated and dried under reduced pressure. Thereby, the title compound (4.91 g) was obtained as a grey solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.28 (s, 2H), 7.46-7.53 (m, 1H), 7.58-7.64 (m, 1H), 7.83 (dd, J = 1.0, 7.9 Hz, 1H), 7.94 (dd, J = 1.0, 7.9 Hz, 1H).

(0237)

## Reference Example 38

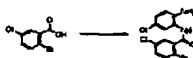
N-(2-amino-4,5-dichlorophenyl)-2-(1H-imidazol-2-yl) benzamide.

The title compound was synthesized using the same process as in Reference Example 33. MS (FAB): 347 (M<sup>+</sup>+1, 30 %).

HRMS (FAB): calcd for C<sub>16</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>4</sub>O 347.0466, Found 347.0462.

(0238)

## Reference Example 39

N-(2-amino-5-chlorophenyl)-2-bromo-5-chlorobenzamide.

The title compound was synthesized using the same process as in Reference Example 33.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 5.30 (s, 2H), 6.59 (dd, J = 2.6, 8.5 Hz, 1H), 6.79 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.48 (dd, J = 2.6, 8.6 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 2.6 Hz, 1H), 9.77 (s, 1H)

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MS (EI): 357 (M<sup>+</sup>, 66 %).

HRMS (EI): calcd for C<sub>13</sub>H<sub>9</sub>BrCl<sub>2</sub>N<sub>2</sub>O 357.9275, Found 357.9280.

Anal, Calcd for C<sub>13</sub>H<sub>9</sub>BrCl<sub>2</sub>N<sub>2</sub>O•0.3H<sub>2</sub>O: C, 42.72; H, 2.57; N, 7.66.

Found: C, 43.08; H, 2.87; N, 7.26.

(0239)

**Reference Example 40**

2-(2-bromo-5-chlorophenyl)-5-chloro-1H-benzimidazole.



Acetic acid (100 ml) solution of N-(2-amino-5-chlorophenyl)-2-bromo-5-chlorobenzamide (5.14 g) was heated to 80°C, and it was stirred for five hours. The reaction solution was concentrated, and produced white solid was washed with hexane and dried under reduced pressure, and the title compound (3.62 g) was obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.28 (dd, J = 2.0, 8.6 Hz, 1H), 7.56 (dd, J = 2.6, 8.6 Hz, 1H), 7.63-7.75 (m, 2H), 7.86 (d, J = 2.6 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 11.98 (br, 1H)

MS (EI): 342 (M<sup>+</sup>, 100 %).

Anal, Calcd for C<sub>13</sub>H<sub>7</sub>BrCl<sub>2</sub>N<sub>2</sub>•0.4H<sub>2</sub>O: C, 44.70; H, 2.25; N, 8.02.

Found: C, 44.52; H, 2.63; N, 7.08.

(0240)

**Reference Example 41**

Ethyl [(4-nitrophenyl sulphonyl) amino] acetate.



At 15°C, 4-nitrobenzene sulphonyl chloride (31.75 g) was added to dichloromethane (500 ml) solution of glycine ethyl ester hydrochloride (20.0 g) and triethylamine (59.8 g). At 25°C, the reaction solution was stirred for ten hours, and next the reaction mixture was transferred to water (800 ml), and the organic layer was separated. The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 3/1). Thereby, the title compound (26.94 g) was obtained as an orange solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.08 (t, J = 7.2 Hz, 3H), 3.80 (s, 2H), 3.97 (q, J = 7.2 Hz, 2H), 8.02-8.08 (m, 2H), 8.37-8.42 (m, 2H).

(0241)

**Reference Example 42**

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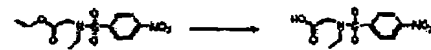


Ethyl [ethyl (4-nitrophenyl sulphonyl) amino] acetate.

To dimethylformamide (50 ml) solution of ethyl [(4-nitrophenyl sulphonyl) amino] acetate (5.95 g) was added sodium hydride (1.07 g, 60% in mineral oil) at 10°C, and the mixture was stirred for 20 minutes. Ethyl iodide (2.47 ml) was added, and it was stirred at 25°C for 18 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (300 ml) and extraction was carried out with ethyl acetate (100 ml). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 2/1). Thereby, the title compound (1.01 g) was obtained as an orange solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.05 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 3.28 (q, J = 7.2 Hz, 2H), 4.03 (q, J = 7.2 Hz, 2H), 4.15 (s, 2H), 8.08-8.12 (m, 2H), 8.36-8.41 (m, 2H).

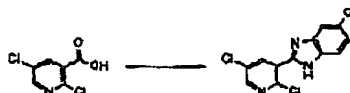
(0242)

**Reference Example 43**[Ethyl (4-nitrophenyl sulphonyl) amino] acetic acid.

2N sodium hydroxide aqueous solution (10 ml) was added to methanol (30 ml) solution of ethyl [ethyl (4-nitrophenyl sulphonyl) amino] acetate (820 mg) and was heated to 80°C, and it was stirred for 15 minutes. The reaction mixture was cooled to 25°C and the reaction solution was transferred to water (200 ml) and extraction was carried out with ethyl acetate (50 ml). The aqueous layer was adjusted to pH5.0 using 6N hydrochloric acid, and extraction was carried out with chloroform (50 ml x 5). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was washed with hexane and dried under reduced pressure, and the title compound (360 mg) was obtained as slightly yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.05 (t, J = 7.2 Hz, 3H), 3.28 (q, J = 7.2 Hz, 2H), 4.05 (s, 2H), 8.06-8.11 (m, 2H), 8.35-8.40 (m, 2H).

(0243)

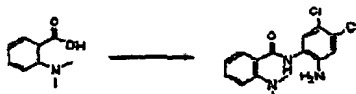
**Reference Example 44**5-chloro-2-(2,5-dichloro-4-pyridinyl)-1H-benzimidazole.

At 25°C, 2,5-dichloropyridine-3-carboxylic acid (5.98 g), 4-chloro-1,2-phenylenediamine (4.45

g), 1-(3-dimethylaminopropyl-3-ethyl carbodiimide hydrochloride (5.98 g) and triethylamine (4.8 ml) dissolved in chloroform (200 ml) solution were stirred for four hours. The reaction solution was transferred to water (700 ml), and the precipitated solid was separated by filtration. This solid was dissolved in nitrobenzene (50 ml) and was heated to 170°C and was stirred. Following cooling to 25°C, it was refined by silica gel column chromatography (hexane / ethyl acetate = 200/1 to 2/1). Thereby, the title compound (3.30 g) was obtained as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.31 (dd, J = 2.0, 8.6 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 1.7 Hz, 1H), 8.52 (d, J = 2.6 Hz, 1H), 8.68 (d, J = 2.6 Hz, 1H), 13.10 (br, 1H).

(0244)

## Reference Example 45

N-(2-amino-4,5-dichlorophenyl)-2-(dimethylamino) benzamide.

The title compound was synthesized using the same process as in Reference Example 33.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.74 (s, 6H), 5.29 (s, 2H), 7.00 (s, 1H), 7.12-7.17 (m, 1H), 7.28-7.31 (m, 1H), 7.45-7.51 (m, 1H), 7.78 (dd, J = 1.6, 7.6 Hz, 1H), 7.92 (s, 1H), 11.17 (s, 1H).

MS (FAB<sup>+</sup>): 324 (M<sup>+</sup>+1, 86 %).

Anal, Calcd for C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O:

C, 55.57; H, 4.66; N, 12.96.

Found: C, 55.62; H, 4.69; N, 12.85.

(0245)

## Reference Example 46

Methyl 2-(diallyl amino) benzoate.

Sodium hydride (47.0 g, 60% in mineral oil) was added to dimethylformamide (1.0 l) solution of methyl anthranilate (77.2 g) cooled to 5°C and was reacted at 5°C for 30 minutes. Allyl bromide (97.2 ml) was added dropwise, and on completion of the dropwise addition, it was reacted at 25°C for 19 hours. The reaction mixture was transferred to water (3.0 l), and extraction was carried out with ethyl acetate (500 ml x 4). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 50/1) and the title compound (65.49 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.67-3.69 (m, 4H), 3.78 (s, 3H), 5.08-5.10(m, 1H), 5.12-5.14(m, 2H),

5.20-5.21(m, 1H), 5.69-5.82(m, 2H), 6.89-6.95 (m, 1H), 7.06-7.09(m, 1H);, 7.32-7.39 (m, 1H), 7.48 (dd, J = 1.6, 7.6 Hz, 1H)

MS (EI): 231 (M<sup>+</sup>, 4 %).

(0246)

**Reference Example 47**

Methyl 2-(dimethylamino) benzoate.



At 25°C, sodium hydride (10.7 g, 60% in mineral oil) was added to dimethylformamide (300 ml) solution of methyl anthranilate (40.0 g) and was reacted at 25°C for 30 minutes. Methyl iodide (18.1 ml) was added dropwise, and on completion of the dropwise addition, it was reacted at 25°C for 18 hours. The reaction mixture was transferred to saturated aqueous sodium chloride solution (1.0 l), and extraction was carried out with ethyl acetate (500 ml x 2). The organic layer was dried with magnesium sulphate, and it was filtered, and thereafter it was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (hexane / ethyl acetate = 10/1) and the title compound (28.6 g) was obtained as light brown liquid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.75 (s, 6H), 3.80 (s, 3H), 6.78-6.84 (m, 1H), 6.96 (dd, J = 1.0, 8.6 Hz, 1H), 7.32-7.39 (m, 1H), 7.50 (dd, J = 1.5, 7.8 Hz, 1H).

(0247)

**Reference Example 48**

Methyl 2-[allyl (methyl) amino] benzoate.



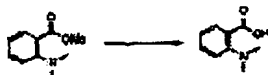
The title compound was synthesized using the same process as in Reference Example 47.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.70 (s, 3H), 3.65 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 5.14-5.22 (m, 2H), 5.76-5.92 (m, 1H), 6.82-6.88 (m, 1H), 6.99-7.02 (m, 1H), 7.33-7.39 (m, 1H), 7.48 (dd, J = 1.9, 7.9 Hz, 1H).

(0248)

**Reference Example 49**

2-(dimethylamino) benzoic acid.



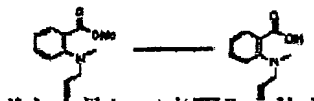
A mixture of methyl 2-(dimethylamino) benzoate (28.6 g), 2N potassium hydroxide aqueous solution (50 ml) and methanol (100 ml) was reacted at 90°C for three days. The reaction mixture was cooled to 25°C and transferred to water (500 ml), and it was neutralized using concentrated hydrochloric acid and extraction was carried out with chloroform (100 ml x 15). The organic layer was dried with magnesium sulphate, and concentration was carried out under reduced pressure after filtration, and the title compound (22.77 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.81 (s, 6H), 7.33-7.39 (m, 1H), 7.60-7.72 (m, 2H), 7.96-7.99 (m, 1H).

(0249)

Reference Example 50

2-[allyl (methyl) amino] benzoic acid.



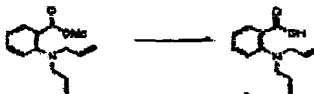
The title compound was synthesized using the same process as in Reference Example 49.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.77 (s, 3H), 3.73 (d, J = 6.6 Hz, 2H), 5.15-5.23 (m, 2H), 5.67-5.86 (m, 1H), 7.32-7.38 (m, 1H), 7.63-7.65 (m, 2H), 7.97 (dd, J = 1.3, 7.2 Hz, 1H).

(0250)

Reference Example 51

2-(diallyl amino) benzoic acid.



A mixture of methyl 2-(diallyl amino) benzoate (65.49 g), 6N potassium hydroxide aqueous solution (80 ml) and methanol (250 ml) was reacted for 13 hours at 80°C. The reaction mixture was cooled to 25°C and transferred to water (1.0 l), and it was neutralized using concentrated hydrochloric acid and extraction was carried out with chloroform (300 ml x 3). The organic layer was dried with magnesium sulphate, and concentration was carried out under reduced pressure after filtration, and the title compound (53.83 g) was obtained as a white solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 3.74-3.77 (m, 4H), 5.11-5.18 (m, 4H), 5.64-5.79 (m, 2H), 7.34-7.40 (m, 1H), 7.61-7.68 (m, 2H), 7.96-7.99 (m, 1H).

(0251)

Preparation Example 1

Each of the following components were mixed in accordance with conventional procedures and thereafter tableted, and 100 tablets containing 50 mg active ingredient per tablet were obtained.

N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-2-hydroxy-N-methylacetamide hydrochloride (5.0 g), carboxymethylcellulose calcium (disintegrating agent) (0.2 g), magnesium stearate (lubricant) (0.1 g), microcrystalline cellulose (4.7 g).

(0252)

**Preparation Example 2**

Each of the following components were mixed in accordance with conventional procedures, and thereafter the solution was sterilised in accordance with conventional procedures, and it was packed into ampoules in an amount of 5 ml, and it was freeze-dried in accordance with conventional procedure, and 100 ampoules containing 20 mg active ingredient per ampoule were obtained.

N-[4-chloro-2-(6-chloro-1H-benzimidazol-2-yl) phenyl]-2-hydroxy-N-methylacetamide hydrochloride (2.0 g), mannitol (20 g), distilled water (500 ml).

(0253)

**Test Example 1**

Activity of the compound of this invention with respect to osteoclast differentiation induction.

**Production of collagen arthritis mouse**

It was carried out in accordance with a process of E.D. Trentham et al. (J. Exp. Med. Vol. 146, pp. 857-69 (1977)). In other words, bovine type II collagen (the collagen training society, CosmoBio) dissolved in acetic acid solution was admixed with Freund's Complete Adjuvant (Freund's Complete Adjuvant 37Ra) (DIFCO), and was intradermally injected into the tail setting part of DBA/1J mice (Japan Charles River). Three weeks later, bovine type II collagen mixed with Freund's Incomplete Adjuvant (DIFCO) was subcutaneously injected into dorsal part as a booster.

**Cell preparation and culture**

It was carried out in accordance with a process of Japanese Journal of Bone Metabolism, Vol. 12, p.188 (1994), Arthritis and Rheumatism, Vol. 39, p.S285 (1996) and Ministry of Health and Welfare rheumatism survey study undertaking study report book, p.130 in 1994. In other words, the tissue of the site at which collagen arthritis was induced, was treated with disperse solution (Godo Shusei), and floating cells were obtained. These cells were prepared into an appropriate concentration with  $\alpha$  MEM ( $\alpha$  minimal essential medium) culture medium including 5 % foetal calf serum, the cells were mixed with test compound using 96 hole culture plate, and thereafter, cultured under condition of 5 % carbon dioxide concentration, 37°C for six days. Formed osteoclast quantity was counted by the method wherein tartaric acid resistant acid phosphatase

staining was carried out, thereafter the cells having at least 3 of stained nuclei were counted under a microscope. The inhibition rate of each compound was determined with making inhibition rate of vehicle as 0 % and the inhibition rate with the number of osteoclast of 0 as 100 %. The results are shown in Table 33. As may be seen from Table 33 that the group of compounds of this invention strongly inhibited osteoclast differentiation induction.

(0254)

Table 33

Osteoclast differentiation induction inhibition ability (Concentration of test compound: 0.1  $\mu$ M)

Test compound	Inhibition rate (%)
Vehicle	0
Example 1	19
Example 12	66
Example 24	89
Example 27	54
Example 55	72
Example 57	70
Example 61	32
Example 63	55
Example 74	58
Example 76	94
Example 82	94
Example 93	76
Example 94	97
Example 99	55
Example 105	69
Example 114	81
Example 116	80
Example 120	53
Example 121	96
Example 127	73
Example 128	97
Example 135	58
Example 142	38
Example 145	71
Example 161	96
Example 168	55
Example 173	75

(0255)

**Test Example 2**

Investigation of onset prevention effect with respect to collagen arthritis of the compounds of this invention.

**Provocation of collagen arthritis**

Collagen arthritis was induced using 6-week-old DBA /1J mice (Japan Charles River) in accordance with process of Test Example 1. Test compound was suspended in 0.5 % methylcellulose solution (MC) and administered once a day continuously for 50 days from the next day of the initial sensitisation to ten animals per group. The dosage was set at 50 mg/kg (per kg of mouse body weight), and only MC was administered to the control group. The administration was carried out by forced oral administration using a tube for mouse.

**Evaluation process**

It was carried out by the arthritis score using the swelling of the joints observed by the naked eye as an indicator and by X-ray score using the destruction image of articulation structure as an indicator.

**Results**

The compound of Example 55 inhibited arthritis score by 65 % compared to the control group. Moreover, this compound also inhibited the rise of X-ray score by 65 %. Moreover, no abnormality was observed whatsoever in body weight, liver weight or other external appearance or the like by the administration of the compound of Example 55. As described above, it was understood that the compound of this invention could inhibit arthritis and the subsequent articulation destruction without serious side effect.

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